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## EDITORIAL

IT will be seen that in the Notes and Comments section in this issue there is a new feature which goes under the heading of "From the Morbidity Conference". In this we have given very short abstracts of interesting cases which have been discussed in those monthly meetings which are held now in several teaching centres, and at which some of the less successful incidents are reviewed with frankness and sincerity. The holding of these meetings indicates an entirely healthy and salutary tendency in the specialty. The anonymous publication of some of the more interesting occurrences, as has been so frequently recommended by Professor Macintosh, should help to prevent the occurrence of similar accidents and to avoid complacency. We would ask those who present material at such Conferences to send us short abstracts of their cases and also any who are less fortunate, in that such monthly meetings are not readily available to them, to consider whether they would not like this column to act as their forum.

# ANTIDOTES TO "TRUE" CURARIZING AGENTS
## including a report on Ro 2-3198 (Tensilon)

By A. G. DOUGHTY and W. D. WYLIE

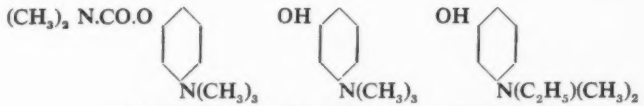
THE need for an antidote to curare-like substances may arise clinically in the following circumstances:

1. To restore full respiratory activity at the end of an operation.
2. To reverse curarization in an unexpectedly short operation, e.g. when prolonged surgery is intended but found to be impracticable.
3. Following a short procedure during which almost complete paralysis of the patient has been necessary.
4. To abolish curarization in a patient who has shown an unusual sensitivity to curarizing drugs, e.g. latent myasthenics.
5. To abolish the occasional long-lasting mild sequelæ of curarization.

Neostigmine is well established as an effective antidote, but it has marked side effects which, while not precluding its use in anæsthesia, justify a search for an equally efficient drug without them.

Randall (1950) investigated a series of 27 compounds for anti-curare activity. Of these he selected two which appeared to approach the ideal of maximum antidotal effect with minimal side-actions. These compounds are known as Ro 2–2561 and Ro 2–3198, the latter being available in the U.S.A. under the trade name of Tensilon. They are closely related to neostigmine, but

they lack the dimethyl carbamic side-chain which is considered to be responsible for the anticholinesterase activity of the latter.




Neostigmine Ro 2–2561 Ro 2–3198 (Tensilon)

In animal experiments Randall found that these substances possess $\frac{1}{4}$ the potency of neostigmine as anticurare agents but appear to have a much less marked stimulating action on the parasympathetic system. In experiments on the electric eel their anticholinesterase activity is only 1/100 that of neostigmine. MacFarlane et al. (1950) report that Ro 2–3198 is only 1/1000 to 1/500 as potent as neostigmine in inhibiting rat's brain cholinesterase. These data suggest that a safer antidote than neostigmine is available, since the disadvantages of neostigmine arise from its powerful muscarinic action.

## CLINICAL TRIALS OF NEOSTIGMINE AND RO 2–3198 (TENSILON)

The advantages and disadvantages of any antidote to a muscle relaxant may be crudely assessed on clinical grounds. That this should be so is important, since the final test of efficiency must be against the background of clinical use. Neostigmine, adequately buffered by atropine sulphate, now occupies a definite place in anæsthesia where muscle relaxants of curariform action are used. By clinically accepted standards it leaves little to be desired as an antidote, but its side effects are considerable and may be

dangerous in certain circumstances. These side effects are noticeable in conscious individuals, and can be assessed on such a person by simple comparison with other drugs of like type. It is also possible to gain some idea of the efficiency of an antidote against a known dose of muscle relaxant on a conscious person.

*Conscious Subjects*

Experiments on conscious subjects were carried out with two objects in mind: first, to record the side effects of clinical doses of neostigmine with and without atropine, and by comparison with these results to assess Ro 2–3198 (Tensilon); second, assuming that the new drug offered certain advantages over neostigmine in regard to these side effects, to assess its value as an antidote against a curarizing agent and by comparison with neostigmine.

The table shows the results of injecting known doses of an antidote into conscious subjects. Subjective symptoms were almost entirely limited to fasciculation of muscles, to epiphora, salivation and intestinal stimulation. Objectively the pulse rate was recorded. In doses up to as much as 20 mg. of Ro 2–3198 symptomatic manifestations were never more than slight, and rapidly passed off, whereas with a dose of 1.25 mg. of neostigmine, previously covered by 1.3 mg. of atropine sulphate, just as obvious manifestations were noticed though with this dose they did not persist. With either drug some degree of bradycardia was present, and this lasted for a longer period than the subjective sensations. Unbuffered neostigmine produced markedly severe and prolonged reactions.

In attempting to assess the efficacy of Ro 2–3198 as an antidote, a dose of gallamine triethiodide (Flaxedil), sufficient to produce diplopia and weakness of the small

*Effects of Ro 2-3198 (Tensilon) and Neostigmine on Conscious Subjects.*

| Subject | Drug | Dose mg. | Symptoms | Duration in minutes | Pulse change |
|---|---|---|---|---|---|
| A | Ro 2-3198 | 5 | 0 | 0 | 0 |
| B | Ro 2-3198 | 5 | + | 3 | − 6/min. |
| A | Ro 2-3198 | 10 | + | 5 | − 10/min. |
| B | Ro 2-3198 | 10 | + | 3 | − 12/min. |
| A | Ro 2-3198 | 20 | + | 4 | − 12/min. |
| B | Ro 2-3198 | 20 | + | 6 | − 12/min. |
| A | Neostigmine | 2.5 | + + + + | 45+ | − 12/min. |
| A | Neostigmine preceded by atropine sulphate | 1.25 +1.3 | + | 10 | − 8/min. |
| A | Neostigmine with atropine sulphate | 2.5 +0.65 | + + | 20 | − 12/min. |
| B | Neostigmine with atropine sulphate | 2.5 +0.65 | + + | 35 | − 14/min. |

muscles of the hands, was given intravenously. This averaged 40–50 mg. Ro 2–3198 or neostigmine was given later, either within two minutes of the onset of curarization or after approximately 15 minutes had passed and the paralyzing effect was rapidly passing. In the former case it was found that the effective dose of Ro 2–3198 was between 15 and 20 mg. but that with this dose there was a liability to revert to partial muscle paralysis after 10–15 minutes. It is emphasized that the assessment of paralysis and the reversal to paralysis was made on a purely subjective basis and largely upon ocular imbalance, which is, however, the earliest symptom of curarization and the last to disappear on recovery. Nevertheless, in comparison with doses of neostigmine varying from 1.25 mg. to 2.25 mg. the prolonged effect of Ro 2–3198 was unsatisfactory.

When given 15 minutes after the gallamine, clinically it was as effective as neostigmine.

*During Anæsthesia*

Clinical assessment of Ro 2–3198 during anæsthesia was made on two types of case. First, when a high concentration of curarizing agent was known to be present in the patient, and second, at the termination of an operation when curarization was still apparent. Electro-convulsive therapy with full muscle relaxation was chosen for the first series. The second series was made up of operations during which a muscle relaxant was used and at the termination of which curarization persisted.

For electro-convulsive therapy the procedure was to use a full paralysing dose of a relaxant after a sleep dose of thiopentone and premedication with atropine sulphate. Such a dose, when gallamine triethiodide is used, averages 140 mg. for a female and 160 mg for a male. After the convulsion, and following the period of apnœa succeeded by attempted spontaneous respiration, it is usual to inject 2.5 mg. of neostigmine and to repeat this if necessary. In a series of thirteen cases, Ro 2–3198 was used in place of neostigmine. Dosage was started at 20 mg. and additional doses up to a maximum of 45 mg. were given. In later cases as much as 40 mg. were given at once. In no case was the subsequent respiration considered adequate, and in every case neostigmine was used when the failure of Ro 2–3198 became apparent. The addition of neostigmine produced clinically marked improvement in every case, and the improvement was sustained.

In the second series, Ro 2–3198 was used on over 50 occasions to restore the tone of the abdominal musculature and thoracic respiration at the end of abdominal operations

in which either d-tubocurarine chloride or gallamine triethiodide was used as the relaxant. In view of the limited effects noted on conscious subjects it was not given with atropine sulphate. The effectiveness as an antidote was judged clinically by hardening of the abdominal muscles and restoration of thoracic respiratory activity.

In those cases in which a relatively small dose of relaxant was given at the beginning of the operation and there were no supplementary doses, the antidotal effect appeared to be complete and recession to the curarized state did not occur. When multiple doses of relaxant were given during the operation the effect of Ro 2–3198 was not reliable: in some cases there was a satisfactory response and no apparent recession to the curarized state, while in others, after an initial response, thoracic respiration appeared to diminish again. The least satisfactory cases were those in which a dose of relaxant was given to facilitate closure of the peritoneum. The Ro 2–3198 would in these cases be given about five minutes after the relaxant.

An attempt was made to assess the effect of the drug on the parasympathetic system. In no case was there excessive salivation or bronchial secretion following its administration in spite of the absence of atropine sulphate. In view of the fact that many of the cases had been given pethidine during the operation its atropine-like action may be responsible for the absence of effects which other workers have observed.

The heart rate was slowed in all cases but the blood pressure remained constant following Ro 2–3198. The fall in pulse rate was greatest when the drug was used to counter the effects of gallamine triethiodide in contrast to d-tubocurarine chloride. This might be expected as the

production of tachycardia is a recognized side-action of the former relaxant.

## ASSESSMENT OF RO 2-3198 (TENSILON)

From clinical experience and from experiments on the conscious subject certain conclusions concerning Ro 2–3198 as an antidote to the curarizing agents can be made.

1. Following an intravenous injection its action begins to take effect within a minute as compared with two minutes for neostigmine.

2. Although Ro 2-3198 is reported to have only one-hundredth the anticholinesterase activity of neostigmine there is no doubt that, in man, subjective symptoms of parasympathetic stimulation occur such as sweating, salivation and intestinal stimulation. It also produces bradycardia. These actions of the drug last a short time, whereas those of neostigmine are sustained. The subjective effect of neostigmine on the bowel may last as long as 45 minutes. This finding with Ro 2–3198 is in accordance with that of Randall, who found that it is comparatively easily washed out of a preparation of the isolated intestine.

3. The short period of action of Ro 2-3198 may lead to recurarization of a patient if its effect wears off before that of the relaxant. Ro 2–3198 is therefore more satisfactory against a relaxant, the effect of which is beginning to wear off, than against a recently injected dose. To our knowledge no case has yet been reported of a return to the curarized state following the use of neostigmine.

4. Clinically Ro 2-3198 is similar in action to neostigmine but lasts a very much shorter time. It is suggested that 20 mg. might be considered equivalent to 2.5 mg. of neostigmine, though the statement of equivalents is misleading unless it is understood to refer only to immediate action rather than long-term.

5. The use of atropine sulphate with Ro 2-3198 is not considered necessary, and in this series has been omitted without ill effect.

### DANGERS OF ANTIDOTES

Stimulation of the parasympathetic nervous system produced by neostigmine may cause salivary and bronchial secretion, bronchial constriction and intestinal colic. While these effects are undesirable, it is the slowing of the heart due to vagal stimulation which may endanger life. Vagal stimulation may cause the heart to stop in diastole, though despite continued stimulation it may start again by the operation of the vagal escape phenomenon.

It is well established that an adequate dose of atropine sulphate should be given in conjunction with neostigmine in order to minimize the latter's muscarinic effect. There is, however, a difference of opinion as to whether the atropine sulphate should be given synchronously with neostigmine or whether it should precede the latter. On theoretical grounds it should be given some 15 minutes before neostigmine because its full vagal blocking effect takes longer to develop than the vagal stimulating effect of neostigmine. Goodman and Gilman (1941) point out that as atropine sulphate has a central stimulating effect it may at first produce a slowing of the pulse owing to its

effect on the vagal centres in the brain. It would thus enhance the very effect of neostigmine which it was intended to reduce. However, the fact remains that even with the doses of atropine sulphate normally used clinically, i.e. 1.3 mg.–0.65 mg., 2.5 mg. neostigmine always produces a slowing of the pulse rate. Furthermore, in the conscious subject the intestinal colic was very little mitigated. These facts are not surprising in the light of Goodman and Gilman's view that doses of 2 mg. are necessary completely to block the vagus in man. Both tubocurarine chloride and gallamine triethiodide block the vagal ganglia and therefore contribute to the protection afforded to the patient by atropine sulphate. It follows that it is less safe to give neostigmine to an uncurarized patient than to a curarized one, and consequently it is essential to ensure that any respiratory depression at the end of an operation is due more to neuromuscular paralysis than to central depression before administering neostigmine.

Patients already under the influence of drugs which produce bradycardia are probably more susceptible to the dangers of neostigmine. Cyclopropane has a direct depressant effect on the conducting tissue of the heart and enhances the effect of neostigmine in producing cardiac arrest and in preventing the operation of the vagal escape phenomenon. Jaundice is associated with bradycardia and it may be more than a coincidence that two of the three recorded deaths associated with neostigmine were in deeply jaundiced patients.

A case described by Macintosh (1949) illustrates the dangers implicit in the use of neostigmine or any vagal-stimulatory drug when the conducting mechanism of the heart is depressed.

A gravely ill man aged 38 years with a pulse of 140 per minute was to be operated on for a perforated gangrenous appendix. Anæsthesia was with thiopentone and cyclopropane. Relaxation was obtained with d-tubocurarine chloride given intermittently in doses of 15 mg., 10 mg. and 5 mg. At the end of the operation the pulse rate was 100 per minute and the tidal exchange was so inadequate that assisted respiration was necessary. 2.5 mg. of neostigmine with 0.65 mg. of atropine sulphate were injected and the patient died within a few minutes.

Clutton-Brock (1949) also describes a death following neostigmine:

The patient, aged 75 years, was deeply jaundiced and had undergone an operation for relief of common bile duct obstruction. Anæsthesia was by Kemithal 1 gramme, d-tubocurarine chloride 25 mg. in divided doses and 50 per cent nitrous oxide and oxygen. Assisted respiration was maintained throughout the operation. Cyclopropane was given at the end of the operation to afford relaxation for peritoneal suture. Neostigmine 2 mg. with atropine sulphate 0.65 mg. was then injected intravenously. Shortly after this the patient became grey and pulseless and died despite cardiac massage. At necropsy the myocardium was said to be in a very poor condition.

These two cases are examples of the association of neostigmine with death under cyclopropane, and with the possibility of jaundice and myocardial degeneration as contributory factors in the latter.

A third fatality associated with neostigmine given as an antidote to d-tubocurarine chloride has been described by Hill (1949):

The patient, a deeply jaundiced baby of 7 weeks, weighing 6 lb. 7½ oz., underwent an operation for congenital atresia of the common bile duct. Anæsthesia was induced with open drop ether and following this a total of 0.9 mg. d-tubocurarine chloride was given. The operation lasted 1½ hours, relaxation was adequate and respiration and pulse were satisfactory throughout. At the conclusion of the operation the child was given an injection of 0.25 mg. of neostigmine and 0.22 mg. of atropine sulphate intravenously. It collapsed almost immediately and died despite remedial measures.

The dose of neostigmine given, 0.25 mg., would be proportional to a dose of 6 mg. for a 70 kg. adult: a very large dose under any circumstances. While it is probable that sheer overdose was responsible for this child's death one may observe in passing that the child was probably no longer under the influence of the d-tubocurarine chloride and that the contributory protective effect of vagal blockage was therefore no longer present. It is interesting to note also the association of this fatality with jaundice.

Very marked vagus bradycardia may be produced even when the heart is apparently not under the influence of other depressive drugs. This is illustrated by the next case.

A 60-year-old man was operated on for diathermy removal of a carcinomatous polyp of bladder and implantation of radon seeds. He had a blood-pressure of 210/140 mm. of mercury but was fully compensated, leading an active life and complaining only of hæmaturia. Premedication was with Omnopon 10 mg. and scopolamine 0.43 mg. and anæsthesia with thiopentone 0.7 gramme and nitrous oxide-oxygen. Pethidine hydrochloride 25 mg. was added towards the end of the operation and 30 mg. of d-tubocurarine chloride were used to produce relaxation. At the end of operation one hour and ten minutes after induction, the blood-pressure was 160/120 mm. of mercury and the pulse rate 90/minute. He was given neostigmine 2.5 mg. and atropine sulphate 0.65 mg. intravenously. Within ten minutes he developed a marked sinus bradycardia of 40 per minute, a fall in cardiac output so that the systolic pressure was with difficulty recorded at 60 mm. of mercury and Cheyne-Stokes type of respiration. He was cyanosed, cold and sweating but able to open his eyes and respond when asked questions. Respiration reverted to normal when he was put on oxygen and an electrocardiogram taken at this point confirmed the condition of sinus bradycardia with a pulse rate of 44/minute. He was given Methedrine 10 mg. intravenously and 10 mg. subcutaneously. 15 minutes later his pulse rate was 77/minute and blood-pressure 180/120 mm. of mercury. He was fully conscious, talking and co-operative. Postoperative recovery was uneventful.

Neostigmine was given at the termination of operation because there was evidence of residual curarization despite adequate respiration. Atropine sulphate was given with the neostigmine, since pethidine had been given previously. Five minutes after the injection the patient was moving and talking, his blood-pressure was near his pre-operative level, and there was no evidence of parasympathetic stimulation as evidenced by salivation, or bronchial spasm, nor was the pulse rate decreased at this point. Gross sinus bradycardia developed on the way back to the ward and within a further five minutes. It is interesting to note the delay in the onset of the effect, and it is fortunate that during the period of collapse no irreversible change took place in the patient. It would have been preferable to have given the atropine sulphate before the neostigmine, but it is by no means certain that such a dose would have prevented the sinus bradycardia.

Neostigmine may be potentially dangerous in ways other than by the causation of cardiac arrest or extreme bradycardia. In conscious subjects atropine sulphate appeared to have little effect in mitigating the severity of the symptoms of bowel stimulation caused by neostigmine. It is held by some that the bowel, overstimulated by neostigmine given at the end of an operation, may be more prone subsequently to develop post-operative ileus. A case has been brought to our notice in which a colostomy was opened immediately at the end of an operation. Neostigmine was given to abolish the remaining curarization. The colostomy "worked" copiously and the patient died of peritonitis.

A further reason for caution in the use of neostigmine is that the increased bronchial secretion which may occur despite the administration of atropine sulphate may be a

factor in the causation of post-operative pulmonary atelectasis. Bronchospasm in susceptible subjects may also follow an injection of neostigmine.

It follows that neostigmine is a potentially dangerous drug despite the large number of occasions on which it has been used without serious consequences. It would therefore be safer not to regard the standard dose of 2.5 mg. as the minimum effective dose, since in many cases as little as 1 mg. has produced the desired effect. A safer policy would be to give an initial dose of 1 mg., preceded of course by atropine sulphate, followed by increments of 0.5 mg. until the desired effect has been obtained.

## DISCUSSION

The introduction into clinical practice of the ultra-short-acting muscle relaxants such as succinyl choline may limit the occasions on which it may be necessary to use neostigmine or other antidotes to curarizing agents. As long as the longer-acting "true" curarizing drugs such as d-tubocurarine chloride or gallamine triethiodide continue to be used, the need for an efficient antidote to their action will remain.

Of the antidotes available neostigmine appears to be the most efficient. Ro 2–3198 has less marked side-actions than neostigmine, but its efficiency, even in very large doses, is limited by its relatively short period of action. American reports suggest that Ro 2–3198 is more effective than neostigmine, but their comparative dose of neostigmine is 0.5 mg., which is very much smaller than the doses usually employed in British practice. A more accurate assessment might be made with electromyographic studies rather than on clinical impressions, but our experience

has shown differences sufficiently great to be appreciated easily by clinical observation.

If the exact mode of action of Ro 2–3198 were known, it might be possible to use the drug with greater effectiveness. Experimental evidence suggests that it does not act by inhibiting cholinesterase. If we accept this evidence, obtained from animal experiments, another explanation for its mode of action must be sought. The fact that reversion to the curarized state can occur in man shows that Ro 2–3198 does not free the curarizing drug from its attachment to the muscle end-plate. In view of its slight but definite parasympathetic stimulant action it would appear that it exerts its antidotal effect by means of a non-specific cholinergic activity.

The search for a specific antagonist to the curarizing agents continues. So far it does not appear that a drug has yet been discovered which will detach curare from the muscle end-plate. The known antagonists appear merely to increase the degree of stimulation at the neuromuscular junction and reversion to the curarized state will occur if the period of action of the antagonist is shorter than that of the curarizing drug. There is no evidence that the known antagonists increase the rate of elimination of the curarizing agents.

SUMMARY

The indications for the use of antidotes to muscle relaxants are enumerated.

The pharmacology of a new drug, Ro 2–3198 (Tensilon), is discussed.

The effects of neostigmine and Ro 2–3198 (Tensilon) on the conscious subject and on patients under anæsthesia are recorded.

The dangers of neostigmine are discussed with reference to known mishaps which have occurred following the use of the drug.

We are indebted to Roche Products Ltd. for generous supplies of Ro 2–3198 (Tensilon) on which part of the subject matter of this paper is based.

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# THIOPENTONE NARCOSIS IN THE PRESENCE OF HEPATIC DYSFUNCTION*

By JOHN W. DUNDEE

IT can be assumed that, if the liver plays a major part in the detoxication of thiopentone, an increase in duration of narcosis will result when the drug is used in the presence of liver damage. Despite the fact that thiopentone has been in use since 1934 its detoxication is still imperfectly understood (Hewer, 1948). Some workers (Carraway and Carraway, 1943) use the drug indiscriminately in the presence of hepatic dysfunction, and report no prolongation of narcosis. Others (Pleasance, 1943) consider liver damage to be an absolute contraindication to the use of thiopentone. It is hoped that the experimental and clinical observations presented in this paper will be a guide to the use of thiopentone in the presence of liver damage, and help to elucidate the part played by the liver in its detoxication.

## A. EXPERIMENTAL DATA

The duration of thiopentone narcosis in animals, before and after liver damage, has been investigated by several workers. Scheifley and Higgins (1940) and Mason and Beland (1945) found no alteration after partial hepatectomy in the rat. Similar results were found by Richards and Appel (1941) using carbon tetrachloride to produce liver damage. On the other hand, Shideman et al. (1947) and Kelly et al. (1947) found an increase in duration of nar-

* Part of a thesis presented for the M.D. degree of The Queen's University of Belfast.

cosis ranging from 751–1169 per cent after the production of liver dysfunction. This liver dysfunction was produced by three methods, (*a*) injection of carbon tetrachloride (mice); (*b*) 80–90 per cent hepatectomy (rats) and (*c*) production of Eck fistula (rats). A smaller, though significant, increase in duration of narcosis (350 per cent) after partial hepatectomy in rats was found by Walker and Wynn Parry (1949). An important feature of their results was that sleeping time tended to return to normal as liver regeneration occurred.

It can be seen that experimental evidence in animals has produced two diametrically opposed views, viz. liver damage has no effect on the duration of thiopentone narcosis and liver damage markedly prolongs the duration of narcosis. Certain seemingly legitimate criticisms as to the methods employed by the earlier workers (Scheifley and Higgins, 1940; Mason and Beland, 1945; Richards and Appel, 1941) have been made by Shideman (1949). These objections, together with the fact that no actual times are given to support their statements, would seem to invalidate the results of the workers who found no increase in duration of narcosis after the production of liver damage in animals.

A significant increase in the duration of the action of thiopentone was found by Shideman et al. (1948) and Shideman (1949) in 6 human subjects with abnormal liver function, as compared with 10 subjects with normal liver function. In the following experiment the duration of action of thiopentone was noted with the same subjects before and after the administration of a hepatotoxic agent, viz. chloroform. This eliminates the variation in response of different individuals which occurred in Shideman's investigation.

*Technique of Experiment*

It has been shown (Mark et al., 1949) that, on administering the same dose of thiopentone to humans at intervals of several days, the corneal reflex always returned at the same plasma level. The return of the corneal reflex was used as the end point, and when it reappeared the time was noted and an additional dose of thiopentone administered. Fourteen fit male volunteer subjects were used for the experiment and liver function was estimated by the bromsulphalein excretion test. Before administration of the chloroform less than 4 per cent of the dye was found in the blood stream 30 mins. after intravenous injection of 2 mg. per kg. body weight; this being taken as evidence of normal liver function (Rosenthal and White, 1925).

No premedication was given and the subjects were induced with 0.4–0.5 g. thiopentone. Following the return of the corneal reflex the time was noted and an additional dose of 0.2–0.25 g. administered. Each time the corneal reflex returned the time was noted and a supplementary dose of thiopentone administered to a total of 1.0–1.5 g.

A clear airway was maintained throughout the administration and it was possible to avoid cyanosis in all subjects without the administration of oxygen.* The rate of injection of thiopentone was kept constant throughout the experiment, viz. 1 ml. 5 per cent solution every 5 seconds.

In 7 of the subjects, once the respiratory excursion had returned to normal, following the last injection of thiopentone, chloroform was administered for 30 minutes, after which the patient was allowed to recover. The remaining subjects were used as controls and no chloroform was administered.

* It is appreciated that this does not exclude the occurrence of anoxia.

The thiopentone was repeated in exactly the same doses as before 48 hours later in 13 subjects, and 24 hours later in 1 subject. The rate of injection was the same as before and the return of the corneal reflex was again used as the end point. Prior to the administration of the thiopentone, liver function was estimated by the bromsulphalein excretion test in 5 of the 7 subjects who received chloroform.

*Results*

There was an increase in the time taken for return of

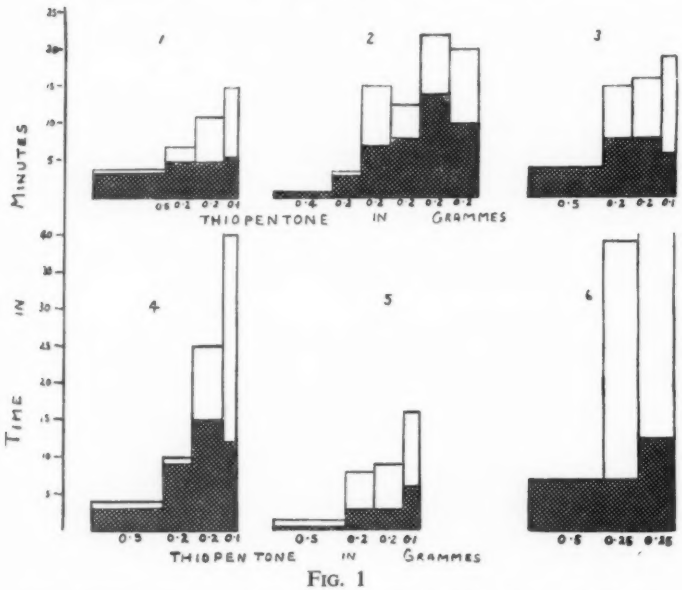


FIG. 1

Diagrammatic representation of the times taken for return of the corneal reflex following intermittent injection of thiopentone in six subjects, before and 48 hours after administration of chloroform. The shaded areas show the times before the administration of the chloroform, the non-shaded areas representing the increase in time at the second administration.

the corneal reflex in all subjects at the second administration of thiopentone. Details of the times in subjects 1–6, i.e. those in whom the second administration followed 48 hours after the chloroform, are shown in figure 1. The sum of the times for all subjects is shown in table I. This table shows a statistical analysis of the total times taken for return of the corneal reflex in subjects 1–6 and 8–13, following the intermittent administration of 1.0 g. thiopentone. In each of the groups the figures are directly comparable and it can be seen that a significant increase occurred in the subjects who received the chloroform, while that which occurred in the controls, although present in all cases, is not statistically significant. Table I verifies that chloroform produced a demonstrable degree of liver dysfunction. This is greater than that obtained by Waters (1951), but in these cases the open mask method of administration was used and the accompanying anoxia may have been a factor (Goldschmidt et al., 1937). Case 7, in whom the second administration followed 24 hours after the first, is not directly comparable to the others and is only included for the sake of completeness.

*Discussion*

From figure 1 it can be seen that the times taken for return of the corneal reflex after the induction dose of thiopentone were barely altered after the administration of chloroform. In 3 cases the increase was very slight for the second dose, but in all cases the increase in time became more marked with each successive dose of thiopentone. Recovery from a small dose of thiopentone is due to a rapid diffusion of the drug to non-nervous tissues (Brooks et al., 1948, 1950; Mark et al., 1949). As repeated doses are administered equilibrium is set up until eventually

TABLE I

*Table showing sum of times taken for return of corneal reflex following intermittent doses of thiopentone in 14 male subjects.*

| CASES RECEIVING CHLOROFORM | | | | | | | | CONTROLS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | Age in yrs. | Thiopentone in grammes | Time in Mins. A | Time in Mins. B | % increase in time 100(B – A) / A | % bromsulphalein retention 5 mins. | % bromsulphalein retention 30 mins. | Subject | Age in yrs. | Thiopentone in grammes | Time in Mins. A | Time in Mins. C | % increase in time 100(C – A) / A |
| 1 | 29 | 1.0 | 19 | 37 | 95 | 35 | 10 | 8 | 54 | 1.0 | 43 | 45 | 2.3 |
| 2 | 32 | 1.4 | 43 | 73 | 75 | 30 | 10 | 9 | 38 | 1.0 | 66 | 99 | 50 |
| 3 | 37 | 1.0 | 26 | 54 | 104 | | | 10 | 23 | 1.1 | 77 | 101 | 30.1 |
| 4 | 25 | 1.0 | 40 | 88+ | 120+ | | | 11 | 25 | 1.5 | 72 | 80 | 11.1 |
| 5 | 44 | 1.0 | 12½ | 42½ | 240 | 37 | 17 | 12 | 28 | 1.0 | 25 | 30 | 20.0 |
| 6 | 40 | 1.0 | 26½ | 96½+ | 270+ | 40 | 17 | 13 | 44 | 1.0 | 53 | 67 | 26.4 |
| 7 | 36 | 1.5 | 10 | 92 | 820 | 85 | 35 | 14 | 44 | 0.8 | 45 | 67 | 48.8 |
| Average times of cases 1-6 for 1.0 g. thiopentone | | | 24 ±3.4 | 58.6 ±4.1 | 144.2 | | | Average times of cases 8-13 for 1.0 g. thiopentone | | | 48.2 ±9.5 | 61.6 ±16.7 | 27.7 |
| S.D. | | | 8.16 | 9.84 | | | | S.D. | | | 13.3 | 23.4 | |
| Coefficient of Variation | | | 34 | 16.7 | | | | Coefficient of Variation | | | 26.9 | 37.8 | |
| Standard error of difference between the 2 averages | | | 5.21 | | | | | Standard error of difference between the 2 averages | | | 11.0 | | |

A. First administration.
B. Exactly 48 hours after administration of chloroform in subjects 1-6, and 24 hours after chloroform in subject 7.
C. Exactly 48 hours after first administration of thiopentone, no chloroform being given.

Percentage bromsulphalein retention shows amount of dye in blood 5 mins. and 30 mins. after injection of 2 mg./kg. intravenously 48 hours after administration of chloroform.

A statistical analysis is included of 6 comparable cases in each series. Average is taken from sum of times taken for return of corneal reflex, following doses of thiopentone totalling 1 g. in each series.

recovery from narcosis depends on detoxication of the drug. From figure 1 it can be concluded that, whatever was the mechanism of prolongation of the time taken for return of the corneal reflex after the administration of thiopentone, it was not interference with diffusion of the drug to the tissues.

This is confirmed by figure 2. For the first 5–10 minutes of the narcosis, during which time the shift of thiopentone from the plasma to the tissues was occurring, there was no significant difference in the amounts of thiopentone required by the subjects at the two administrations. However, at 30 minutes, the subjects who had received

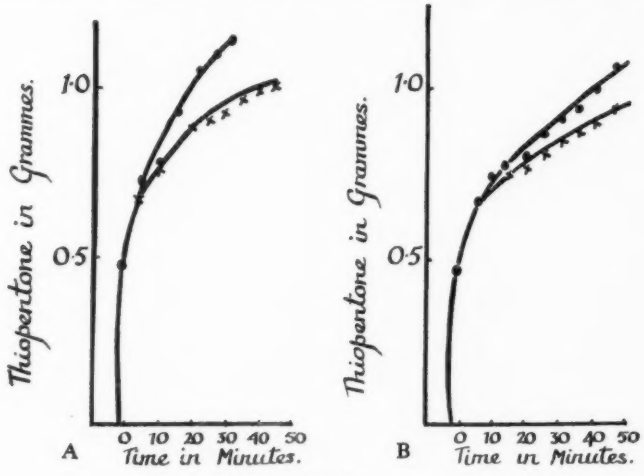


FIG. 2

Graphic representation of average amounts of thiopentone required by six subjects to produce anæsthesia of sufficient depth to obtund corneal reflex, on two occasions 48 hours apart.

A. Chloroform was administered for 30 mins. following the first thiopentone.

B. Controls, to whom no chloroform was administered.

•—•—• First administration of thiopentone.

×—×—× Second administration of thiopentone 48 hours later.

chloroform required much less drug on the second administration (0.3 g), than did those not having chloroform. By this time diffusion of the drug to the tissues would be fairly complete (Mark et al., 1949), save that to fat (Mark et al., 1950). Since return of the corneal reflex signified that the plasma thiopentone had reached a certain level—the same for each subject—it follows that by some means or other the detoxication of thiopentone is impaired by the previous administration of chloroform.

Hepatic dysfunction was certainly present in these subjects in whom detoxication of thiopentone was impaired (table I). However, chloroform is a general protoplasmic poison (Gould, 1949), with deleterious effects on kidneys and blood (Adriani, 1946). These latter could have played a part in the impairment of the detoxication mechanism of thiopentone. Its effects on the central nervous system must also be considered. Barbital is known to be excreted unchanged in the urine, its duration of narcosis being unaffected by partial hepatectomy (Pratt, 1933), yet narcosis with it became prolonged and more profound 24 hours after the administration of chloroform (Koppanyi et al., 1936). Although it was completely eliminated from the central nervous system, the chloroform may have sufficiently injured the nerve cells to render them more susceptible to the action of the barbiturate. This "extrahepatic factor" (Koppanyi et al., 1936) may have played a part in the prolongation of narcosis in cases 1–7. The longer the time that elapses between the administration of the chloroform and the barbiturate the less important would it be. The difference between the degree of prolongation of narcosis in case 7 (820 per cent) and cases 1–6 (average 144 per cent) could be due to this effect of the chloroform on the central nervous system, since the

second administration of thiopentone in the former case took place 24 hours before that in the others.

*Conclusions*

These experiments prove that chloroform impairs the detoxication of thiopentone. This impairment occurs in the presence of demonstrable hepatic dysfunction, but it cannot be assumed that this dysfunction is the sole cause of the decreased rate of detoxication of the thiopentone.

### B. CLINICAL DATA

The same controversy exists in the clinical reports of the administration of thiopentone in subjects with hepatic dysfunction as in the experimental evidence to which reference has already been made. No prolongation of narcosis was reported by Ruth et al. (1939) following the administration of thiopentone for laparotomy in the presence of massive cancer of the liver. They do not mention the dose of the drug used. Lundy (1942), although not advising the use of the drug on purely theoretical grounds in patients with liver dysfunction, has found that such patients tolerate thiopentone satisfactorily. The Carraways (1939, 1943) similarly find that thiopentone is a satisfactory anæsthetic agent for subjects with liver disease.

On the other hand, prolonged narcosis has been reported by Miller and Tovell (1940) in cases in which thiopentone was given in the presence of considerable hepatic dysfunction. Macintosh and Bannister (1947) report a slight prolongation of narcosis in jaundiced patients. Sherlock (1950) stresses that short-acting barbiturates are detoxicated slowly in the presence of liver disease and are safe only in small doses for the induction of anæsthesia.

The purpose of the present investigation is to discover

if subjects with marked liver damage require less thiopentone than normal subjects to produce surgical anæsthesia. The amounts of thiopentone and d-tubocurarine chloride required to produce satisfactory operating conditions in a series of subjects having upper abdominal operations were noted at five-minute intervals. All subjects received $\frac{1}{6}$ gr. (10 mg.) morphia and 1/100 gr. (0.65 mg.) atropine as premedication. The anæsthetic technique was the same for all cases, viz. balanced light anæsthesia with thiopentone, d-tubocurarine chloride, nitrous oxide-oxygen (1 litre each per minute), respiration being controlled or assisted throughout as required. Supplementary doses of thiopentone were given in increments of 0.05 g., so that, after the effect of the induction dose had worn off, at no period had the subject received a dose of thiopentone which exceeded the minimal requirements to produce satisfactory anæsthesia by this amount.

Subjects were divided into three groups: (*a*) normal subjects, (*b*) subjects with a mild degree of hepatic dysfunction and (*c*) subjects with severe liver damage. Because of the diversity of its functions, any single laboratory test, devised as a means of assessing hepatic function, only tests one or a group of related functions and must not be taken as an indication of the liver with respect to other of its functions (Glynn, 1949). For this reason positive findings were required in a series of tests before a subject was proven to have liver dysfunction. With three or more of the following findings a subject was considered to have severe liver damage, while one or two only were taken as evidence of mild hepatic dysfunction.

(*a*) History of recent severe attack of jaundice.

(*b*) Urinary urobilinogen present to a dilution greater than 1 in 20.

(*c*) Thymol turbidity of more than 4.
(*d*) Cephalin cholesterol + + + or + + + +.
(*e*) Diminished serum albumin/globulin ratio.
(*f*) Liver damage shown by biopsy.

Subjects in whom any factor occurred which might influence the response to thiopentone were excluded from the series. These included a raised blood urea (Richards et al., 1950), severe anæmia—Hb under 70 per cent, or marked hypotension. Where shock or severe blood loss occurred during the operations observations were restricted to the period before this happened.

*Results*

The average findings for each group of subjects are shown in table II and figure 3. It can be seen that subjects with severe hepatic damage required much less thiopentone to produce anæsthesia for 60 minutes than did normal subjects. Before deciding whether the difference between the figures is significant, other factors will have to be

TABLE II

*Comparison of Anæsthetic Requirements for Upper Abdominal Surgery in 3 groups of Patients all anæsthetized with the same technique.*

| Group | A | | B | | C | |
|---|---|---|---|---|---|---|
| No. of Cases | 121 | | 31 | | 21 | |
| Average Age | 46 yrs | | 49 yrs. | | 52 yrs. | |
| | T | C | T | C | T | C |
| Induction | 0.52 | 17.2 | 0.50 | 15.5 | 0.38 | 18 |
| Up to 15 mins. | 0.75 | 20.07 | 0.73 | 21.0 | 0.47 | 23.3 |
| „ „ 30 „ | 0.88 | 24.45 | 0.81 | 25.0 | 0.50 | 26.5 |
| „ „ 45 „ | 0.92 | 27.2 | 0.87 | 26.7 | 0.52 | 28.5 |
| „ „ 60 „ | 1.04 | 29.2 | 0.91 | 28.0 | 0.54 | 30.0 |

A = Normal Subjects
B = Subjects with Moderate Liver Damage
C = Subjects with Severe Liver Damage

T = Total dose of thiopentone administered in g.
C = Total dose of d-tubocararine administered in mg.

considered. d-Tubocurarine chloride is known to have no effect on the duration of thiopentone narcosis (Paulson and Essex, 1949; Gray et al., 1951), yet it may be argued that administration of large doses of relaxant will decrease the dose of thiopentone required to produce good operating

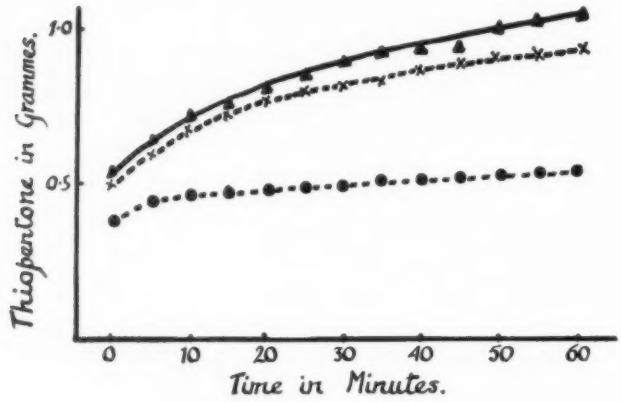


FIG. 3

Graphic representation of average thiopentone requirements of three groups of subjects during upper abdominal operations.
△—△—△ Normal subjects.
×—×—× Subjects with mild hepatic dysfunction.
•—•—• Subjects with severe liver damage.

conditions. That this did not occur in this series can be seen from table II, where the average amounts of d-tubocurarine chloride are approximately the same for each group. The average age for each group of subjects does not vary significantly, but unfortunately the weights of all subjects were not recorded. Of the 121 normal subjects, the average weight of 80 was 132 lb.; only 7 of the subjects with mild liver dysfunction were weighed (average 128 lb.) while the average for 17 of the 21 subjects with severe liver damage was 140 lb.

A statistical analysis of average thiopentone requirements for all cases is shown in table III. No significant difference exists between the thiopentone required by the normal subjects and those with a mild degree of liver dysfunction—standard error of difference between two mean values for 60 minutes being .075. Comparing the requirements for normal subjects and those with severe liver damage, apart from the induction dose, subjects with severe liver damage require a significantly smaller amount of thiopentone; the difference being more marked as the duration of the operation proceeds. The difference between the two means for one hour is 7 times the standard error of difference. These figures leave no doubt that subjects with a severe degree of liver dysfunction require less thiopentone than normal subjects to produce satisfactory

TABLE III

*Statistical analysis of Average Requirements of Thiopentone required to produce Surgical Anæsthesia in 3 groups of Subjects referred to in text.*

| | Normal Subjects | Subjects with Liver Damage | |
|---|---|---|---|
| | | Mild | Severe |
| No. of Cases | 121 | 31 | 21 |
| Induction dose | 0.52 ± 0.02 | 0.50 ± 0.02 | 0.38 ± 0.30 |
| S.D. | 0.18 | 0.11 | 0.14 |
| Coeff. of Variation | 36.7 | 22 | 37 |
| Anæsthesia for 15 mins. | 0.75 ± 0.02 | 0.73 ± 0.064 | 0.47 ± 0.012 |
| S.D. | 0.175 | 0.35 | 0.085 |
| Coeff. of Variation | 23 | 48 | 17.8 |
| Anæsthesia for 30 mins. | 0.88 ± 0.01 | 0.81 ± 0.05 | 0.50 ± 0.023 |
| S.D. | 0.09 | 0.28 | 0.11 |
| Coeff. of Variation | 9.8 | 35 | 22 |
| Anæsthesia for 60 mins. | 1.04 ± 0.02 | 0.91 ± 0.029 | 0.54 ± 0.023 |
| S.D. | 0.27 | 0.16 | 0.11 |
| Coeff. of Variation | 38.6 | 17 | 20.5 |

anæsthesia. This is well illustrated by details of the 21 cases with severe liver dysfunction shown in table IV.

*Discussion*

Failure to find a marked difference in the amount of thiopentone required by any of the three groups of subjects to produce anæsthesia for 10–15 minutes, shows that diffusion of the drug from plasma to tissues occurs normally in the presence of hepatic dysfunction. Tolerance, however, is comparatively unaffected in cases with mild liver dysfunction, but is markedly decreased in the presence of gross hepatic damage. No extraneous factors were present in these subjects, which could have interfered with detoxication of thiopentone, other than liver damage. The findings in subjects in whom demonstrable liver damage occurs, but who, for the purpose of this investigation, were classified as having mild hepatic dysfunction, could explain some of the anomalies reported in the literature. The body contains liver tissue far in excess of the minimal amount necessary for normal physiological function (Wright, 1942). The degree of liver dysfunction present must be very great before a subject shows diminished tolerance to thiopentone. This applies particularly to short operations.

*Conclusions*

Considering these findings in the light of previous evidence it can safely be concluded that the liver plays a major role in the detoxication of thiopentone. However, a severe degree of liver damage must be present before this decrease in detoxicating power is clinically manifested. This conclusion is in agreement with the *in vitro* experiments of Dorfman and Goldbaum (1947) and Shideman et al. (1947), in which incubation of thiopentone with liver resulted in a degradation of the thiobarbiturate. A similar

TABLE IV

*Details of 21 patients with severe hepatic dysfunction referred to in text.*

| Evidence of Liver Dysfunction | | | | | | | | | | Anæsthetic | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Flocculation tests | | | | | | Duration of Operation | Thiopentone in g. | | |
| Sex | Age | History of Jaundice | Urinary Urobilinogen | Thymol Turbidity | Cephalin Cholesterol | Serum Alkaline Phosphatase | A/G Ratio | Confirmed by Biopsy | Hrs. Mins. | Induction | Total | Total d.t.c. in mg. |
| F | 33 | yes | 1 : 20 | 16 | + + + | 52 units % | 0.7/1 | yes | 1 0 | 0.5 | 0.6 | 28 |
| F | 60 | yes | | 1 | + + | 35 units % | | yes | 1 0 | 0.35 | 0.4 | 30 |
| M | 46 | yes | normal | 7 | + + + | 15 units % | 0.62/1 | yes | 1 30 | 0.4 | 0.7 | 25 |
| F | 52 | no | normal | 5 | + + + + | 5 units % | | yes | 2 10 | 0.5 | 0.8 | 40 |
| M | 49 | no | 1 : 40 | 3 | + + + + | 17 units % | 1.21/1 | yes | 1 0 | 0.35 | 0.6 | |
| F | 69 | yes | 1 : 80 | | | | | yes | 1 0 | 0.4 | 0.6 | 13 |
| M | 69 | yes | 1 : 40 | | | | | yes | 1 10 | 0.4 | 0.6 | 25 |
| F | 25 | no | 1 : 100 | 3 | + + + | | | | 1 15 | 0.5 | 0.7 | 25 |
| F | 22 | yes | | 9 | + + + + | 15 units % | 1.3/1 | yes | 2 0 | 0.3 | 0.65 | 45 |
| F | 61 | yes | | 4 | + + + + | 85 units % | 1.1/1 | | 1 40 | 0.3 | 0.65 | 30 |
| F | 57 | yes | 1 : 100 | | | | 1.1/1 | | 1 0 | 0.4 | 0.5 | 15 |
| M | 52 | yes | | 1 | + + + + | 95 units % | 1.3/1 | | 1 10 | 0.3 | 0.5 | 40 |
| M | 69 | yes | normal | 1 | — | 70 units % | 1.25/1 | | 1 50 | 0.3 | 0.55 | 40 |
| M | 65 | yes | | 1 | — | 52 units % | 1.5/1 | yes | 2 0 | 0.2 | 0.65 | 47 |
| M | 60 | yes | 1 : 50 | 7 | + + + | | | | 1 20 | 0.5 | 0.65 | 30 |
| F | 46 | yes | | 16 | + + + + | 14 units % | 1.28/1 | yes | 2 30 | 0.3 | 0.6 | |
| F | 60 | yes | 1 : 100 | 7 | + + + | 8 units % | | yes | 2 30 | 0.4 | 0.8 | 45 |
| F | 43 | yes | 1 : 50 | 1 | + + + + | 6 units % | 0.79/1 | yes | 2 15 | 0.3 | 0.5 | |
| F | 49 | no | normal | 2 | + + + + | 7 units % | | yes | 3 45 | 0.45 | 0.9 | 40 |
| M | 60 | no | | 7 | + + + + | | | yes | 1 0 | 0.4 | 0.4 | 28 |
| M | 29 | no | 1 : 50 | | | | | yes | 1 0 | 0.5 | 0.5 | 25 |

breakdown has been reported with the heart-lung-liver preparation (Kelly and Shideman, 1949) and with cell-free homogenate of liver (Gould and Shideman, 1951). Other tissues, e.g. blood (Richards, 1947) and kidney (Kelly et al., 1947; Dorfman and Goldbaum, 1947) may well play a part, but this will not be discussed here.

### C. THE USE OF THIOPENTONE IN THE PRESENCE OF HEPATIC DYSFUNCTION

In anæsthetizing subjects with liver damage, the amount of thiopentone required during the first 10–15 minutes of the operation is approximately that which one would expect to use in a normal subject of similar weight. As anæsthesia progresses the supplementary doses of the drug are required much less frequently than normal. The decreased tolerance to thiopentone in subjects with severe liver dysfunction only becomes clinically obvious after prolonged administration of intermittent doses of the drug.

It is not advisable to administer large doses of thiopentone for induction of anæsthesia for short operations in subjects whose liver function is under suspicion. When plasma-tissue equilibrium has occurred, the amount of the drug remaining in the plasma may well be above that required to produce narcosis. This will have to be removed by the slow process of detoxication, which may be markedly impaired, and prolonged narcosis ensue. The following cases illustrate this point.

*Case* 1. Male aged 32, wt. 147 lb. (67 kg.). Admitted to hospital with compound fracture of tibia and fibula. Surgical toilet carried out under thiopentone-nitrous oxide-oxygen-ether anæsthesia. Exact amount of thiopentone given not known, but thought to be in the region of 1 g. Anæsthesia was uneventful with no delay in recovery.

Five days later the fracture required re-manipulation. The patient felt ill; temperature was 102°F., pulse 90/min. He was

shivering and complaining of pain in both loins. 0.4 g. thiopentone was given quickly to produce relaxation, followed by 0.3 g. three minutes later. At the end of the operation he was deeply unconscious and a pharyngeal airway was inserted. He showed no reaction to supraorbital pressure three hours after his operation and he did not cough out the airway for a further two hours. Consciousness was not regained until 18–19 hours after the thiopentone adminis.ration.

Jaundice appeared on the day following operation, and his subsequent progress proved this to be due to Weil's disease. The leptospira icterohæmorrhagica was later recovered from the urine.

In Weil's disease the liver is severely damaged. The jaundice is probably due to a toxic hepatitis (McNee, 1920). Changes in the liver vary from cloudy swelling to acute parenchymatous degeneration (Dawson et al., 1917; Himsworth, 1947). The onset of hepatic dysfunction is the most feasible explanation for the altered response to thiopentone which this subject exhibited at the second administration.

*Case* 2. A male aged 32 was admitted to hospital from the out-patient department because of delayed recovery following incision of a paronychia under thiopentone anæsthesia. The dose again was not known, but was said to be " just over half a gramme ". It appeared that this patient requested thiopentone instead of gas as he had been given it on several previous occasions with no ill effects. When he gained consciousness 6 hours later he had symptoms of acute gastritis and was kept under observation with the tentative diagnosis of acute cholecystitis. The diagnosis of infective hepatitis was eventually made and 8 days later liver function tests produced the following results.

| | |
|---|---|
| Van den Bergh | biphasic reaction |
| Serum bilirubin | 11 mg. per cent |
| Thymol turbidity | 6 units |
| Cephalin cholesterol | ++++ |
| Urinary urobilinogen | slight excess |

The association of symptoms of acute gastritis and acute hepatitis is well known (Bank and Dixon, 1946) and it is

easy to understand how a tender liver led to the diagnosis of acute cholecystitis. The liver lesion in infective hepatitis is usually mild in nature (Lane, 1942), but it is difficult to postulate any other possible cause for the delayed recovery, other than its being due to hepatic dysfunction.

Another factor which must be considered is the possibility of a toxic action of the thiopentone on an already damaged liver. This has been observed in dogs by Walton et al. (1950), but they attributed their findings to the hypoxia which accompanied the respiratory depression following the thiopentone. The effect of thiopentone on liver function will be the subject of a later communication.

SUMMARY

1. Liver damage produced experimentally by chloroform significantly prolongs the duration of thiopentone narcosis in man.

2. Clinical observations show that subjects with severe hepatic dysfunction require much less thiopentone to produce anæsthesia for long operations than normal subjects.

3. A mild degree of hepatic dysfunction does not materially affect human tolerance to thiopentone.

4. Evidence is submitted to implicate the liver as the major site for detoxication of thiopentone in man.

I am deeply indebted to the 14 volunteers who took part in the experiment described and without whose co-operation this investigation would not have been possible. My thanks are also due to Doctors C. M. Valliant and E. T. Downham who provided facilities for this experiment, and to the many surgeons who permitted me to anæsthetize the cases with liver damage described.

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# THE EFFECT OF CERTAIN ANÆSTHETIC AND RELAXANT AGENTS ON CIRCULATORY DYNAMICS

By F. J. PRIME and T. CECIL GRAY

THE object of this paper is to describe the effects of the commonly used anæsthetic (ether, cyclopropane and thiopentone) and newer relaxant (gallamine triethiodide, decamethonium iodide and Win 2747) agents on cardiac output. The investigations consisted in the first place of animal experiments to demonstrate the effects of these substances on the Starling heart-lung preparation in dogs, and secondly, observations were carried out on human patients during anæsthesia.

## 1. THE EFFECT OF ANAESTHETIC AND RELAXANT AGENTS ON THE CARDIAC OUTPUT, AS MEASURED IN THE STARLING HEART-LUNG PREPARATION IN DOGS

*Method*

Twelve heart-lung preparations were made following the procedure originally described by Knowlton and Starling (1912). Blood clotting was prevented by the use of heparin. Two dogs were used for each experiment, the first being bled under either light ether or thiopentone anæsthesia, in order to fill the reservoir of the perfusion apparatus. Approximately 500 ml. of blood was usually obtained. The dog from which the preparation was to be made was anæsthetized with light ether anæsthesia, followed by chloralose (0.1 mg. per kg.). Heparin was injected just prior to connecting the animal to the external circuit.

In all the experiments the aortic and venous (inferior vena caval) pressures were measured and recorded on a kymograph. The left ventricular output was measured directly by estimating the time in seconds required to fill a 50 ml. graduated cylinder with blood flowing from the distal end of the artificial peripheral resistance. Heart rate was counted immediately after each determination of cardiac output. In all experiments the volume of the circulating blood was 300/500 ml. and its temperature 35° C. The initial condition of the preparations was entirely satisfactory, as judged from the activity of the heart and the venous pressure level, which normally remained almost at zero. The lungs were inspected at frequent intervals in order to observe their condition, in particular to see whether pulmonary oedema was occurring. All the experiments were completed within two hours of making the preparation.

Thiopentone and the relaxants were introduced into the preparation by direct injection into the superior vena cava, and in each instance were preceded by injections of similar volumes of saline as controls. The rate of injection was standardized in each instance. In no case did the injection of these volumes of saline produce any effect upon the heart. When it was desired to administer ether or cyclopropane this was effected by connecting the inflow tube of the respiratory pump either to a Douglas bag containing the anæsthetic mixture, or alternatively, in the case of ether, to an Oxford vaporizer which delivered vapour of approximately known concentration.

In all cases oxygen was given with the anæsthetic. Before the introduction of the anæsthetic respiration was carried out by the pump with an atmosphere of air or oxygen.

## RESULTS

(a) *Ether*

The results of six experiments in which the preparation was submitted to varying concentrations of ether vapour in oxygen were uniform. They are best exemplified by the description of two of the experiments. The data obtained in the other four are summarized in table I.

*Experiment* 3. Male dog weighing 7.5 kg. The initial measurements after the preparation was working steadily were: heart rate 144 per min., aortic pressure 125 mm. of mercury, venous pressure – 3.5 cm. saline and left ventricular output 188 ml. per min. Peripheral resistance was kept constant at 105 mm. of mercury. Ether was given through the respiratory pump. Analysis of the gas mixture given showed an ether concentration of 1.1 per cent. No appreciable effect was observed in the ensuing 15 minutes so the ether concentration was increased to 1.5 per cent. In just over 1 minute (see figure 1) venous pressure started to rise, reaching a plateau at – 2.5 cm. saline. Coincidently, left ventricular output fell to 175 ml. per min., the other measurements remaining unaltered. The concentration of ether in the arterial blood was found to be 25 mg. per 100 ml. After the elapse of 5 minutes the concentration of ether was increased to 2 per cent. Again a rise of venous pressure was recorded. Left ventricular output, which had gradually risen to nearly the initial value, fell to 175 ml. per min. and continued to fall to a steady value of 170 ml. per min. during the next 5 minutes. The other measurements were still unaffected. Blood ether concentration had risen to 33 mg. per 100 ml. Ether having been cut off, the lungs of the preparation were ventilated for 15 minutes with air, when the measurements all returned to their initial levels.

This experiment indicated a degree of failure of the heart during etherization inasmuch as the normal relationship of venous pressure to left ventricular output was reversed; a rise in the former was accompanied by no significant change or a small fall in left ventricular output.

In the following experiment the same phenomenon is exemplified rather differently.

TABLE I

*The effect of insufflation of three concentrations of ether vapour on the dynamics of the dog heart-lung preparation. Experiments* 1, 2, 5 *and* 6. *In these experiments the procedure of Experiment* 3 *was followed (see text).*

| Expt. No. | Conc. of Ether | Heart Rate | R.A.P. cm. saline | Aortic Pressure mm. Hg | Cardiac Output ml./min. | Remarks |
|---|---|---|---|---|---|---|
| 1 | 0 | 145 | 0 | 125 | 150 | Progressive deterioration after 15 min. on 10% ether. |
| | 2% | 145 | 0 | 125 | 150 | |
| | 5% | 130 | 1.0 | 125 | 125 | |
| | 10% | 98 | 3.0 | 100 | 40 | |
| 2 | 0 | 128 | −0.5 | 120 | 236 | After 10 mins. on 5% ether full recovery did not occur when ether withdrawn. R.A.P. constant at + 1.0 cm. |
| | 2% | — | — | — | — | |
| | 5% | 140 | 1.5 | 90 | 130 | |
| | 10% | 120 | 4.5 | 80 | 90 | |
| 5 | 0 | 156 | 0 | 115 | 260 | Blood ether: 30 mg. % 73 mg. % 150 mg. % |
| | 2% | 160 | 0 | 115 | 240 | |
| | 5% | 156 | 2.0 | 115 | 160 | |
| | 10% | 100 | 4.0 | 110 | 100 | |
| 6 | 0 | 130 | 0 | 115 | 135 | Insufflation of 10% ether caused a progressive deterioration. The mean values over the first 10 mins. are given. |
| | 2% | 130 | 0 | 115 | 125 | |
| | 5% | 110 | 2.0 | 115 | 100 | |
| | 10% | 130 | 3.5 | 90 | 80 | |

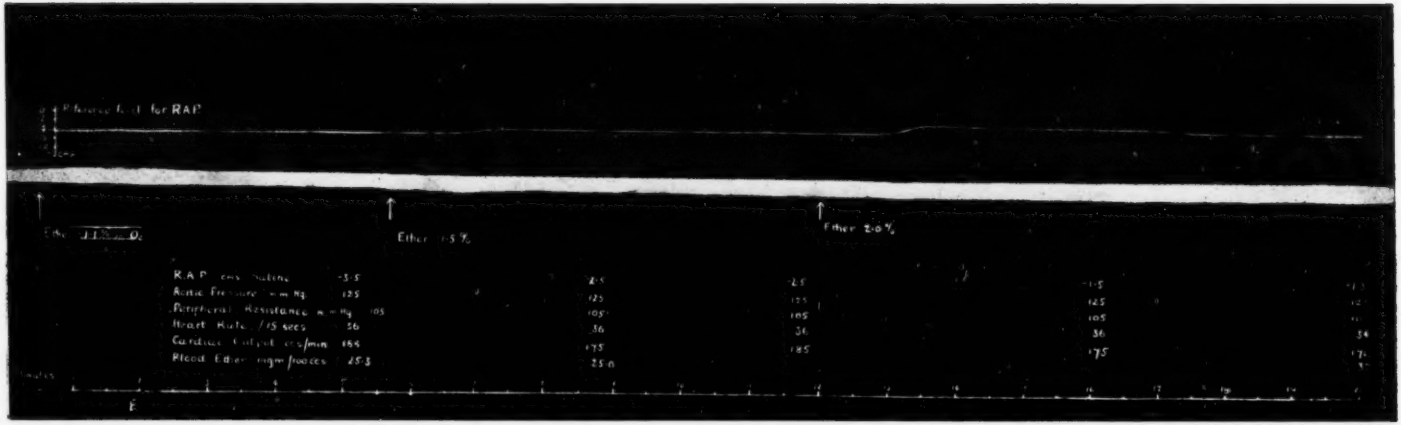


FIG. 1
Showing the effect of ether on the hæmodynamics of the dog heart-lung preparation.

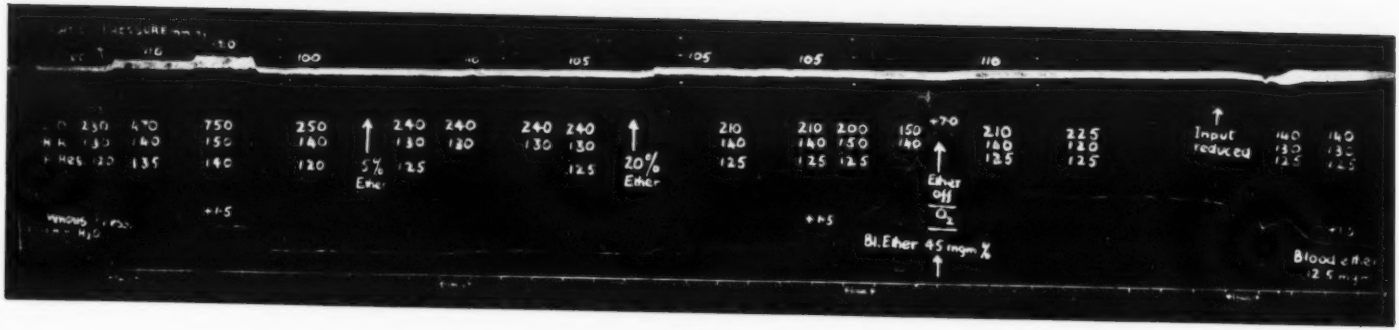


FIG. 2
Showing the effects of greater concentrations of ether on the hæmodynamics of the dog heart-lung preparation.

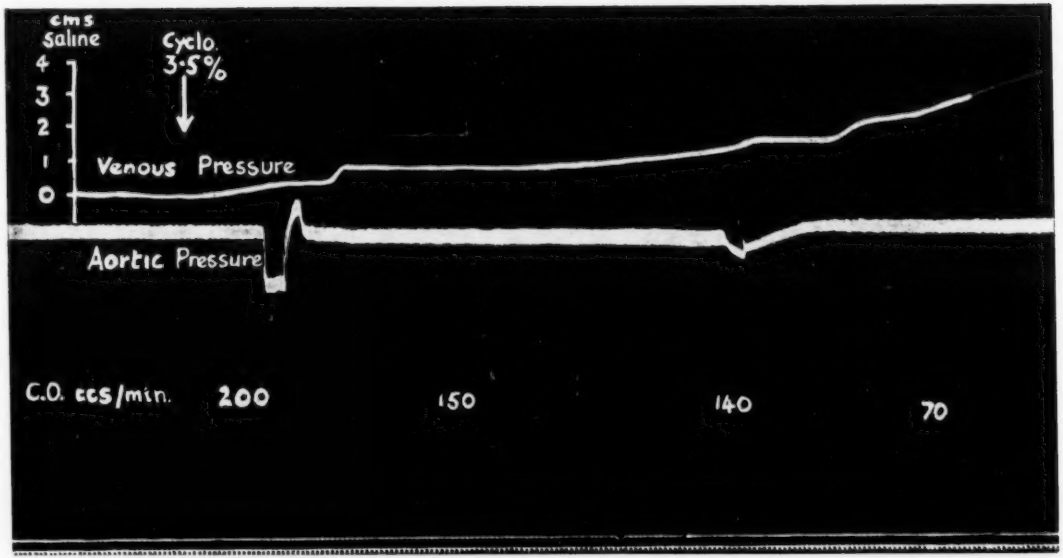


FIG. 3
Effect of insufflation of 3.5% of cyclopropane in $O_2$ on the hæmodynamics of the dog heart-lung preparation.

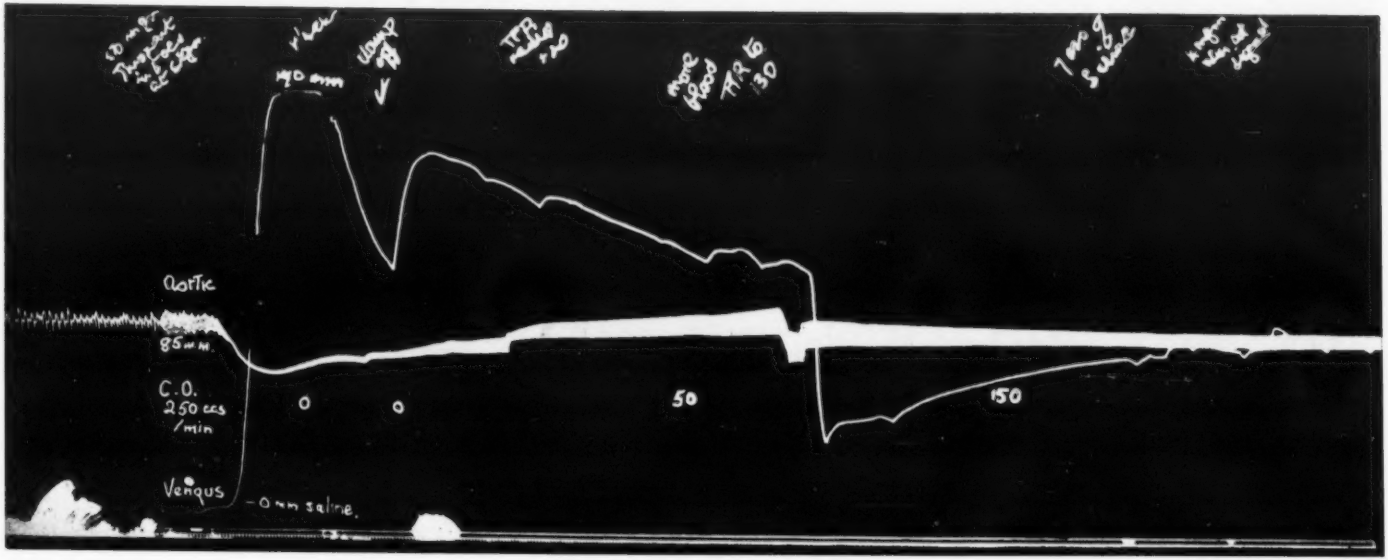


FIG. 4
Effect of the injection of thiopentone on the dog heart-lung preparation.

*Experiment* 4 (figure 2). Male dog weighing 7.5 kg. Initially, when the preparation was ventilated with room air the data were as follows: heart rate 130 per min., aortic pressure 100 mm. of mercury, venous pressure 0 cm. of saline, left ventricular output 230 ml. per min. The right auricular pressure was then raised to +1 cm. of saline by opening the clamp on the venous input. The heart rate was then 140 per min., the aortic pressure 110 mm. of mercury and the left ventricular output rose to 470 ml. per min. The right auricular pressure was further increased to +1.5 cm. of saline, when the heart rate rose to 150 per min., aortic pressure to 120 ml. of mercury and the left ventricular output to 750 ml. per min. (This response was in accordance with Starling's Law of the Heart.) The right auricular pressure was now reduced to zero and the initial values for heart rate, aortic pressure and left ventricular output were again obtained. After a few minutes to allow the preparation to stabilize, ether was admitted to the ventilating pump in a concentration of 5 per cent in oxygen. A small rise (less than 1 cm. of saline) in venous pressure occurred, but there was no change in left ventricular output during the ensuing ten minutes. The concentration of ether was now increased to 20 per cent in oxygen, when the venous pressure immediately started to rise and during the ensuing ten minutes reached a level of +7 cm. of saline. During this time the left ventricular output fell to 150 ml. per minute, and the aortic pressure to 105 mm. of mercury. There was no change in the heart rate. At this time the blood ether concentration was 45 mg. per cent. The preparation was now insufflated with air and an immediate fall in right auricular pressure resulted and coincidently the left ventricular output rose from 150 to 225 ml. per min. and the heart rate fell from 140 to 120 per min. Aortic pressure was restored to 110 mm. of mercury. After approximately 5 minutes the right auricular pressure had become stabilized at +4 cm. of saline. The venous inflow was now reduced until the right auricular pressure remained steady at +1.5 cm. of saline, thus reproducing the conditions of the first part of the experiment. The heart rate was then 130 per min. and the left ventricular output was steady at only 140 ml. per min. The blood ether level was 12.5 mg. per cent.

In the latter experiment a comparison was made between the effects on left ventricular output of altering the right auricular pressure by (*a*) increasing the rate of venous inflow and (*b*) the administration of ether. It will be observed that the response in the latter instance was

opposite to that which occurred in the first place, namely, a rise of venous pressure produced by ether resulted in a fall of left ventricular output instead of, as in the former instance, a rise. Furthermore, at the end of the experiment, with a right auricular pressure of +1.5 cm. of saline, the left ventricular output was only one-fifth of that produced by a rise of right auricular pressure to the same level prior to the administration of ether.

(b) *Cyclopropane*

Cyclopropane produced the same qualitative effects as were seen with ether. The following experiment exemplifies the findings.

*Experiment* 8 (figure 3). Male dog weighing 8 kg. When the lungs were ventilated with air the conditions of the preparation were stabilized as follows: heart rate 160 per min., aortic pressure 125 mm. of mercury, right auricular pressure 0 cm. of saline, and the left ventricular output 200 ml. per min. A mixture of cyclopropane 3.5 per cent in oxygen was admitted to the pump. Within 10 seconds the venous pressure commenced to rise; the heart was observed to be swelling slightly and several showers of extrasystoles occurred. The right auricular pressure continued to rise steadily during the next 15 mins., at the end of which it had still not reached a plateau; the right auricular pressure was still rising after 15 mins., the last reading obtained being +4 cm. of saline. The mean aortic pressure fell to 120 mm. of mercury, but the occurrence of extrasystoles produced sharp temporary falls of greater magnitude. The left ventricular output fell progressively from the initial 200 ml. per min. to 70 ml. per min. at the end of the 15 minutes period. (The blood cyclopropane concentration was 23.4 mg. per cent.)

Four other similar experiments confirmed these results and demonstrated that concentrations of cyclopropane less than 3 per cent produced effects on the heart-lung preparation similar to those exhibited by ether in a low concentration.

(c) *Thiopentone*

*Experiment* 12 (figure 4). Male dog weighing 9 kg. Initial data: heart rate 140 per min., aortic pressure 85 mm. of mercury, right auricular pressure 0 cm. of saline, left ventricular output 250 ml. per min. After an injection of 5 ml. of saline there was no alteration in the above data. Fifty mg. of thiopentone dissolved in 5 ml. of saline were then injected. The response was dramatic. The right auricular pressure rose in the course of 15 seconds to 17 cm. of saline, whilst the aortic pressure fell to 50 mm. of mercury. The left ventricular output fell rapidly and progressively to zero. The heart was greatly dilated and in order to prevent complete collapse of the preparation the venous inflow was clamped off. A fairly rapid fall of right auricular pressure to about 9 cm. of saline resulted, and there was gradual recovery in aortic pressure. The output, however, remained negligible. When the right auricular pressure had reached 10 cm. of saline it was considered safe to readmit venous blood to the preparation, whereupon the right auricular pressure rose again to approximately 12 cm. of saline, and then commenced to fall. The fall was accelerated by lowering the peripheral resistance from 130 to 110 mm. of mercury. An increase in the left ventricular output now occurred. Eventually the peripheral resistance was raised to its initial level (130 mm. of mercury). The left ventricular output was then 50 ml. per min., i.e., one-fifth of its original value, and the right auricular pressure was approximately +8 cm. of saline. The aortic pressure reading was restored to 85 mm. of mercury and remained steady to the end of the experiment. The venous inflow was again cut off. A further fall in right auricular pressure resulted, but this time the aortic pressure was unaffected. The output gradually increased until it reached 150 ml. per min. When the venous inflow was allowed to increase the right auricular pressure gradually rose to a steady value of +7 cm. of saline.

This result, which was reproduced in four other experiments, demonstrated in a convincing fashion the profoundly depressing action of thiopentone on the myocardium and confirmed previous findings (Gray and Gregory, 1948). Incidentally it demonstrated experimentally the beneficent effect of venesection in some forms of cardiac failure.

(d) *The Relaxant Agents*

The effects of gallamine triethiodide, decamethonium iodide and a new agent, Win 2747, on the heart-lung preparation, were investigated. Control injections of saline produced no effect on the preparation, nor did doses of gallamine triethiodide up to 80 mg., decamethonium iodide up to 10 mg. or Win 2747 up to 6 mg. In several instances these substances were also injected into preparations in which the heart had been damaged by previous treatment with ether or, in the case of Win 2747, thiopentone. No alteration in the state of the preparation following administration of these relaxant drugs was observed.

## 2. INVESTIGATIONS ON HUMAN SUBJECTS

No patients were submitted to investigation in whom any abnormality of the cardiovascular system could be detected, e.g. hypertension, arteriosclerosis, or any form of heart disease. Likewise, patients were rejected who showed signs of chronic pulmonary disease which resulted in any degree of arterial sub-oxygenation or dyspnœa of effort. The average age of the subjects was 35 years, the youngest was 17 and the oldest 57. All were males.

### METHODS

(a) *Cardiac Output*

This was determined by cardiac catheterization following the technique described by McMichael and Sharpey-Schafer (1944). The catheters used were made of telcothane and had a bore of rather more than 1 mm. The catheters were passed through an arm vein into the right auricle and from thence into the right ventricle, from which samples of mixed venous blood were obtained. Immediately after withdrawing mixed venous blood, a

sample of arterial blood was taken through a needle which was inserted into the brachial artery, where it was allowed to stay throughout the experiment. A trochar was inserted into this needle after withdrawing blood in order to maintain its patency in full. A-V oxygen differences were determined by a modification of Exton's method (Prime, 1952).

Oxygen consumption was measured on several occasions during the experiment whenever the blood samples were being withdrawn. The methods used were two. That employed most commonly was the spirographic one. In this oxygen consumption was not measured until the patient had been well stabilized on an anæsthetic mixture of constant composition. The spirometer was flushed through and then filled with the gaseous mixture. A simple arrangement of taps allowed the patient to breathe from this spirometer instead of the anæsthetic apparatus: oxygen was admitted by a fine flowmeter at such a rate that the spirogram was horizontal. After recording for about four minutes the patient was again connected to the main anæsthetic circuit and oxygen was allowed to continue flowing into the spirometer, thus giving a record of the rate of inflow, which was evidently equivalent to the oxygen uptake of the patient (figure 5). This method was equally applicable in the case of apnœic patients, the spirogram here being represented by a steady line instead of the usual tooth-combed pattern. No alteration in arterial oxygen saturation can be detected during a minute and a half when oxygen consumption is measured by this latter method, provided the anæsthetic mixture contains at least 50 per cent of oxygen. As a check against this method Douglas bags were used on several occasions. At the start of the estimation one empty bag was attached to the outflow side

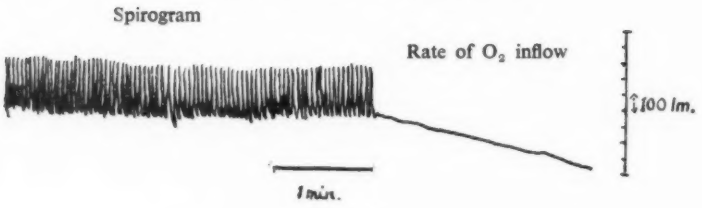


FIG. 5

Spirogram to illustrate method of determining oxygen consumption in patients breathing anæsthetic gas mixtures.

of a non-return valve, whilst a bag full of anæsthetic mixture was attached to the inflow side. The patient breathed from the latter into the former. Two gas meters were used, one to measure the volume of inspired gas, the other to measure the volume of expired air. Samples of both gases were analysed in the modified Haldane apparatus (Prime, 1950) for their oxygen content. From these data oxygen consumption per minute could be calculated. The two methods gave comparable answers.

All determinations of cardiac output were made in duplicate in order to determine as far as possible the errors inherent in the method. The results of these estimations are shown in the Appendix, where it will be seen that difference of the order of 1 litre per minute in cardiac output may be regarded as significant.

(b) *Peripheral Blood-Flow*

Forearm muscle flow was estimated by means of a simple forearm plethysmograph constructed after the pattern described by Lewis and Grant (1925–26). No attempt was made to control the temperature of the forearm because such temperature control was considered (*a*) to be inconvenient and (*b*) to interfere with the effects which we wished to observe by imposing an environment upon the

arm vessels tending to stabilize the vascular tone and hence the blood flow. The effect of such stabilization might be to make the observed muscle flow dependent solely upon changes in cardiac output or blood-pressure. Air was used as the conducting medium and, as a check on volume changes recorded, the temperatures inside the plethysmograph and in the recording device were measured by means of thermocouples. These temperatures remained substantially constant. Where any gross difference was seen the result was either discarded or corrected. The plethysmograms were recorded by an ink writer on a kymograph.

(c) *Blood-Pressure*

Blood-pressure was measured by means of a mercurial manometer attached to a standard brachial cuff except in a few instances where a simple mercurial manometer attached to a hypodermic needle inserted into the brachial artery was used.

## RESULTS

Four groups of data were obtained from each experiment.

1. Determinations of cardiac output before the administration of premedication while the patient was in bed in the ward.

2. The observations were repeated about 1 hour after the premedication was given and about a quarter of an hour before the induction of anæsthesia. In addition, forearm blood-flow was measured at this time.

3. Further measurements of cardiac output and forearm blood-flow were made 10 minutes after induction of anæsthesia.

4. Lastly, the measurements were repeated at intervals during the operation.

A. *d-Tubocurarine chloride followed by thiopentone, nitrous oxide and oxygen*

Fifteen patients were in this group, 12 of whom underwent operation for inguinal hernia and 3 for peptic ulcer.

The initial values for cardiac output were within normal limits, i.e. 4.8 ± 0.86 litres per minute with a mean arterio-venous oxygen difference of 49.4 ml. per litre of blood (table II). Central venous pressure measured relative to the sternal angle was –3.6 cm. saline.

TABLE II

*Showing values for A-V difference, cardiac output, blood-pressure and heart rate in 15 subjects at rest in bed 2 hours prior to induction of anæsthesia.*

| A-V diff. ml./ litre | C.O. ml./mim. | Art. Blood-Pressures mm. Hg | Heart rate per min. |
|---|---|---|---|
| 112.0 | 2.9 | 140/80 | 70 |
| 103.0 | 3.5 | 140/85 | 68 |
| 51.0 | 5.5 | 140/75 | 65 |
| 32.1 | 6.8 | 130/85 | 64 |
| 36.0 | 5.0 | 120/90 | 62 |
| 54.0 | 5.1 | 120/90 | 60 |
| 59.0 | 5.1 | 125/80 | 70 |
| 64.5 | 4.8 | 135/75 | 76 |
| 64.5 | 4.6 | 125/80 | 62 |
| 54.7 | 5.3 | 140/80 | 65 |
| 59.6 | 5.2 | 140/85 | 75 |
| 87.0 | 3.9 | 135/75 | 72 |
| 77.2 | 4.6 | 125/60 | 60 |
| 60.2 | 4.9 | 130/85 | 60 |
| 54.0 | 5.0 | 130/80 | 70 |
| mean | 4.8 ± 0.9 | | 67 ± 5 |

After premedication arterio-venous differences were all lowered, as was oxygen consumption. As a result of these changes cardiac output was, on the average, higher at this

time than the initial measurements. The mean value was 6.7 ± 1.14 litres/min. Heart rate also was somewhat higher than before and in general corresponded with the alterations in cardiac output (table III). Central venous pressure

TABLE III

*Showing values for cardiac output, forearm muscle blood-flow (F.B.F.,) blood-pressure, and heart rate in the 15 cases of Table II after premedication had been administered.*

| C.O. litres/min. | F.B.F. ml./100 ml. forearm/min. | B.P. | Heart rate per min. |
|---|---|---|---|
| 6.7 | 7.5 | 140/80 | 80 |
| 9.2 | 5.5 | 135/85 | 78 |
| 6.0 | 5.0 | 145/80 | 72 |
| 6.8 | 5.0 | 130/90 | 64 |
| 6.2 | 6.0 | 120/90 | 68 |
| 5.6 | 6.0 | 120/80 | 68 |
| 4.2 | 4.0 | 125/85 | 74 |
| 8.3 | 6.5 | 135/70 | 80 |
| 5.9 | 5.0 | 125/75 | 60 |
| 6.7 | 4.5 | 140/85 | 68 |
| 9.1 | 5.5 | 140/75 | 78 |
| 7.0 | 5.0 | 135/80 | 75 |
| 6.4 | 5.5 | 130/65 | 64 |
| 5.8 | 6.0 | 125/80 | 65 |
| 6.3 | 5.0 | 130/85 | 72 |
| mean 6.7 ± 1.14 | 5.5 ± 0.8 | | 71 ± 6 |

showed no consistent change. These higher values should not be interpreted as the effect of premedication but as due to cortical influence aroused by the anticipation of the ordeal to come. This effect can be marked as Stead and his co-workers have shown (Stead et al., 1945).

Blood-pressures measured at this time were all within normal limits and again no consistent alteration was observed from the initial readings.

Estimations of forearm blood-flow showed a good deal of variation between one patient and another, but were fairly constant in each individual. The mean rate of flow

for the whole group was 5.5 ml. per minute per hundred ml. of forearm. Although morphine usually raises blood-flow above this level, in these cases the effect of anxiety on the part of the patient probably tended to lower the mean value and also account for the scatter of the replicate readings. An example of the variability may be taken from case 1 where mean blood-flow was $7.5 \pm 1.2$ ml./min./100 ml. forearm (coeff. of variation = 16 per cent).

After the induction of anæsthesia measurements of cardiac output show a tendency to fall towards initial levels, from which they differ insignificantly (table IV).

TABLE IV

*Showing values for cardiac output, forearm muscle blood-flow (F.B.F.), blood-pressure and heart rate in the 15 subjects of Table II after the induction of anæsthesia with d-tubocurarine chloride, thiopentone and nitrous oxide.*

| C.O. litres/min. | F.B.F. | B.P. | Heart rate per min. |
|---|---|---|---|
| 3.8 | 18.0 | 130/60 | 90 |
| 4.5 | 16.5 | 130/80 | 88 |
| 6.0 | 19.0 | 145/75 | 80 |
| 6.3 | 22.0 | 125/70 | 78 |
| 4.5 | 18.0 | 110/75 | 80 |
| 5.0 | 12.5 | 120/75 | 74 |
| 4.0 | 17.5 | 120/70 | 82 |
| 6.5 | 16.5 | 125/75 | 92 |
| 4.3 | 16.5 | 125/75 | 76 |
| 5.3 | 17.0 | 145/90 | 80 |
| 5.0 | 17.5 | 140/80 | 90 |
| 4.8 | 13.5 | 130/75 | 93 |
| 5.5 | 14.5 | 135/70 | 74 |
| 5.0 | 20.5 | 135/80 | 72 |
| 4.8 | 28.5 | 120/70 | 74 |
| mean $5.0 \pm 0.77$ | $17.5 \pm 3.7$ | | $82 \pm 7$ |

By contrast, forearm blood flow showed a sharp increase closely following upon the injection of the thiopentone. The increase in each case was greatest immediately after the injection and fell slowly during the ensuing ten

minutes or so, and would presumably have returned to the initial level as the effect of the thiopentone wore off. This tendency may be illustrated from the results obtained in case 4. From an initial value of 5.0 ml./min./100 ml. forearm the flow rose to an average of 9.0 ± 1.4 ml./min.; the individual readings fell steadily from 11 ml./min. to 6.8 ml./min. A similar example is shown diagrammatically in figure 6 where the flows were measured for a longer period.

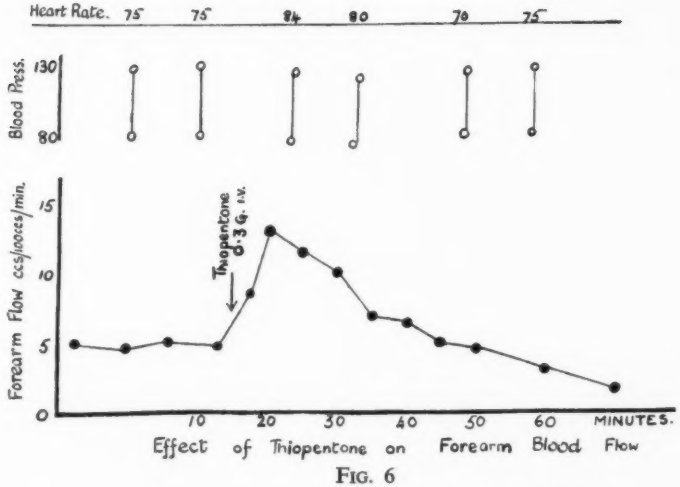
Heart Rate. 75 75 84 80 70 75
Blood Press. 130 80
Forearm Flow ccs/looces/min. 15 10 5 0
Thiopentone 0.3 G. I.V.
10 20 30 40 50 60 MINUTES.
Effect of Thiopentone on Forearm Blood Flow

FIG. 6

Blood pressures showed an initial slight fall with a widening of pulse pressure in most of the cases, though these changes were not great.

Heart rate was increased in all cases, the mean rate being 82 ± 7, i.e., an increase of about 10 beats per minute.

Oxygen consumption was not greatly altered during this part of the experiments; if anything it tended to fall.

The last group of observations taken during operation

are given in summary in table V. The principal changes occurred in forearm blood-flow, which continued to decline to values below the original ones; in some subjects this fall was so marked that the estimates were not very reliable.

TABLE V

*Showing the means of three sets of observations of cardiac output, forearm muscle blood-flow (F.B.F.), blood-pressure and heart rate made at 15-minute intervals during the first hour of operation on 15 subjects under d-tubocurarine chloride, thiopentone and nitrous oxide anæsthesia.*

| C.O. litres/min. | F.B.F. | B.P. | Heart rate per min. |
|---|---|---|---|
| 3.0 | 8.0 | 135/65 | 88 |
| 4.3 | 6.5 | 130/75 | 88 |
| 5.5 | 5.5 | 140/75 | 78 |
| 6.0 | 5.0 | 130/75 | 80 |
| 4.5 | 7.0 | 110/70 | 72 |
| 4.0 | 8.0 | 115/65 | 76 |
| 3.5 | 7.0 | 120/75 | 80 |
| 6.0 | 7.0 | 130/80 | 90 |
| 4.0 | 6.0 | 120/70 | 78 |
| 5.0 | 4.0 | 140/85 | 84 |
| 4.7 | 6.0 | 140/80 | 92 |
| 4.3 | 6.5 | 130/70 | 97 |
| 5.2 | 4.5 | 135/70 | 70 |
| 5.0 | 6.0 | 130/80 | 76 |
| 4.2 | 4.0 | 120/75 | 72 |
| mean $4.6 \pm 0.8$ | $6.1 \pm 1.3$ | | $81 \pm 8$ |

Cardiac output was maintained at normal or slightly lower than normal levels.

Similarly heart rates remained fairly constant at the level achieved after induction.

Blood pressure showed a tendency to fall a little, except in one case where it fell off considerably. Since this case shows an interesting phenomenon, namely a vaso-vagal attack in an unconscious patient, the observations are given graphically in detail (figure 7). The effect occurred towards

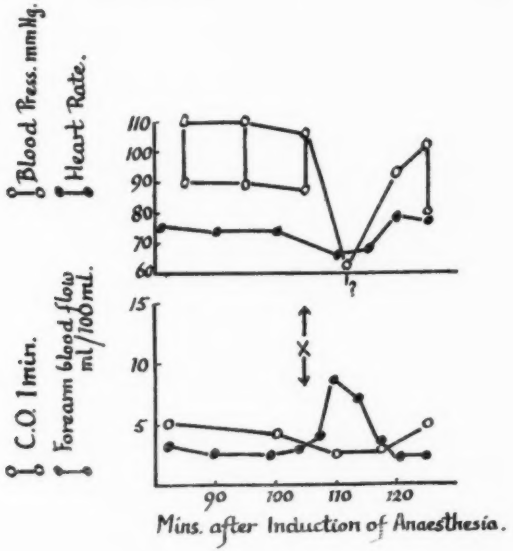


FIG. 7
Vaso-vagal syncope under anæsthesia. This phenomenon was observed during operation (partial gastrectomy) in a man aged 38 years, under thiopentone and nitrous oxide anæsthesia. At X the patient was seen to be moving his fingers.

the end of the operation, a partial gastrectomy, when the anæsthetist lightened the level of anæsthesia by decreasing the percentage of nitrous oxide administered. The patient, who had been quiet up to that time, started to move his hands about and his facial muscles also moved, though he was not actually conscious. His skin was cool and dry. Blood pressure started to fall rapidly from 110/90 mm. Hg to 70 mm. Hg systolic, the diastolic not being obtainable. Coincident with this change the heart rate became slower, cardiac output fell and peripheral blood flow was doubled. This state of affairs continued for about

two minutes, after which the blood pressure rose and forearm flow fell to their previous levels, and the heart rate increased. Had it not been that the effect of lightening anæsthesia was being sought, this change would probably have been missed. It is not the usual result of this procedure and the same effect has not since been obtained. The changes are similar to those occurring after fainting due to acute blood loss described by Barcroft et al. (1944).

B. *Thiopentone followed by ether or mixtures of nitrous oxide, oxygen and ether*

The ten patients in this group all underwent operation for herniotomy. In five of the cases ether was administered with the Oxford vaporizer so that the approximate concentration of ether in the inhaled mixture was known. In the remaining five, the anæsthetic was delivered from a Boyle's apparatus and gas samples were taken from the bag of a Magill attachment for subsequent determination of ether concentration. Samples of arterial blood, drawn when required for cardiac output estimation, were divided into two portions, one for determination of oxygen content and the other for ether concentration. The latter was estimated using the method described by Knox and Pask (1950); the blood required for this was delivered into the digestion apparatus immediately after withdrawal so as to avoid loss of ether by storage of the sample under oil.

The initial measurements of cardiac output, heart rate, blood pressure and forearm muscle blood-flow were made after premedication had been given. The results with their standard deviations are given in table VI. It will be noted that these do not differ significantly from the results given for the previous group.

TABLE VI

*Showing values for cardiac output, forearm muscle blood-flow, blood-pressure, heart rate and mean right auricular pressure in 10 subjects premedicated before induction of anæsthesia with ether.*

| C.O. 1/min. | F.B.F. ml/100 ml/min. | Blood Pressure mm. Hg | Heart rate per min. | Mean right auricular pressure cm. saline |
|---|---|---|---|---|
| 6.2 | 8.0 | 110/80 | 76 | 0 |
| 5.6 | 6.5 | 120/85 | 72 | −3 |
| 6.7 | 9.5 | 125/85 | 65 | −2 |
| 8.2 | 8.0 | 130/80 | 76 | 0 |
| 5.0 | 6.5 | 125/90 | 80 | −4 |
| 4.8 | 5.0 | 120/80 | 66 | 0 |
| 6.3 | 5.5 | 135/75 | 68 | 0 |
| 6.5 | 7.0 | 110/75 | 82 | −1 |
| 5.9 | 7.0 | 115/80 | 68 | −1 |
| 5.7 | 6.0 | 120/85 | 60 | −4 |
| Mean ±S.D. | 6.1±0.9 | 6.9±1.2 | 120/80 | 71±7 | −1.5±1.6 |

The induction of anæsthesia produced early changes in cardiac output and forearm blood-flow, both of which were raised (table VII). The arterial blood pressure accompanying these changes usually showed some widening of pulse pressure but the exact extent of this change is difficult to evaluate by the method used to measure it. Anæsthetists will be familiar with the change often noticeable in the sounds associated with the diastolic point when blood pressure is estimated by the auscultatory method in patients anæsthetized with ether. The characteristically thudding sounds heard in the conscious subject are often replaced by a more muffled sound gradually diminishing as the diastolic point is passed, but lacking the sharp alteration in quality and intensity which is the usual guide to the diastolic level. Some experiments were performed having as their object the elucidation of this difficulty. Forearm blood-flow and cardiac output were artificially

TABLE VII

*Showing values for cardiac output, forearm muscle blood-flow, blood-pressure, heart rate and right auricular mean pressure approximately 15 minutes after induction of ether anæsthesia in the 10 cases of Table VI.*

| C.O. l/min. | F.B.F. ml/100 ml/min. | B.P. mm. Hg | H.R. per min. | R.A.P. cm. saline |
|---|---|---|---|---|
| 8.2 | 28.0 | 115/80 | 85 | 0 |
| 11.0 | 26.0 | 120/80 | 80 | −2 |
| 9.3 | 28.0 | 135/80 | 84 | −2 |
| 7.4 | 20.0 | 135/75 | 80 | +1 |
| 8.6 | 25.0 | 130/90 | 88 | −2 |
| 9.0 | 38.0 | 120/75 | 90 | −1 |
| 8.0 | 30.0 | 135/75 | 86 | 0 |
| 5.8 | 48.0 | 120/75 | 90 | −1 |
| 6.8 | 30.0 | 130/80 | 80 | −1 |
| 9.5 | 28.0 | 125/75 | 75 | −3 |
| Mean ±S.D. 8.4±1.4 | 30.1±7.4 | | 83±5 | −1±1 |

raised by exercising conscious subjects in the hope of producing a similar phenomenon. These manœuvres were not successful, however. The reason for this change, which is important from the clinician's point of view, must await fuller investigation. It seems probable that the values taken for diastolic blood pressure in these cases were inaccurately measured and may be too high; the diastolic point was taken as the level where the sounds were most intense, regardless of their quality.

The acceleration of blood-flow both central and peripheral found shortly after induction was not maintained indefinitely but fell off during the subsequent hour until values lower than the initial ones were reached. This range of values is indicated in the third table of this series (table VIII).

A graphical summary of an individual case is given in figure 8.

TABLE VIII

*Showing range of values for cardiac output, forearm muscle blood-flow, arterial blood-pressure, heart rate and right auricular mean pressure in 10 subjects anæsthetized with ether. Columns (i), (ii) and (iii) give the values measured at approximately quarter-hour intervals beginning half-an-hour after induction of anæsthesia. Column (ii) is omitted in the case of blood-pressure, heart rate and right auricular pressure.*

| C.O. 1/min. | | | F.B.F. ml/min/100ml | | | B.P. mm. Hg | | Heart rate per min. | | R.A.P. cm. saline | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (i) | (ii) | (iii) | (i) | (ii) | (iii) | (i) | (iii) | (i) | (iii) | (i) | (iii) |
| 8.2 | 6.1 | 4.0 | 20 | 10 | 3 | 115/80 | 105/70 | 75 | 68 | 0 | −1 |
| 5.0 | 6.2 | 4.5 | 22 | 18 | 8 | 120/85 | 110/80 | 78 | 70 | −2 | 0 |
| 8.3 | 7.0 | 5.0 | 20 | 15 | 6 | 130/85 | 110/80 | 86 | 80 | −2 | −1 |
| 6.8 | 6.0 | 5.5 | 18 | 5 | ? | 135/80 | 120/75 | 74 | 70 | +1 | 0 |
| 8.5 | 8.0 | 6.5 | 22 | 13 | 7 | 130/90 | 125/90 | 80 | 90 | −2 | −2 |
| 7.8 | 6.8 | 6.3 | 30 | 19 | 11 | 120/75 | 110/70 | 85 | 75 | −1 | −2 |
| 6.3 | 5.8 | 4.2 | 24 | 17 | 6 | 130/70 | 115/80 | 80 | 88 | 0 | +1 |
| 6.0 | 4.5 | 3.8 | 32 | 18 | 9 | 120/80 | 120/85 | 90 | 86 | −1 | −2 |
| 6.2 | 5.7 | 4.1 | 21 | 12 | 5 | 130/85 | 120/80 | 78 | 75 | −3 | −4 |
| 8.9 | 8.0 | 6.8 | 16 | 9 | 3 | 120/80 | 115/85 | 80 | 85 | −3 | −2 |

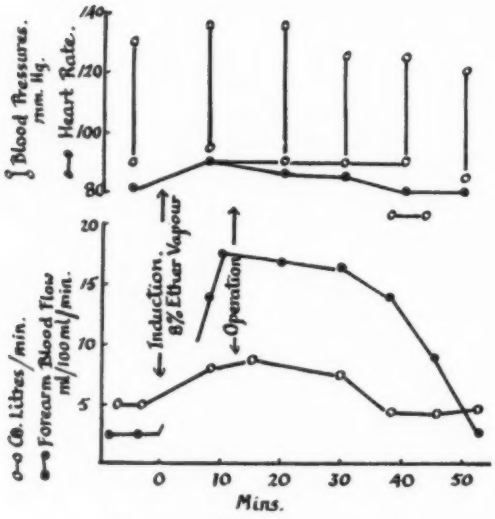


FIG. 8
Effect of ether anæsthesia on cardiac output (C.O.), forearm muscle blood-flow, blood-pressure and heart rate. M. æt 38. Rt. inguinal herniotomy.

*Relationship of dosage with ether to cardiac output*

It was thought likely that heavy dosage with ether might reduce cardiac output from the beginning. In all cases arterial blood ether was determined but no satisfactory correlation of cardiac output with blood ether concentration was obtained except in two cases where the etherization was deliberately pushed to the stage of respiratory arrest when the cardiac output was found to be decreasing along with the arterial blood pressure; in one of these cases the arterial blood ether was 100 mg. per hundred ml. and in the other 160 mg. per hundred ml. The collected data are shown in the form of a scatter diagram (figure 9).

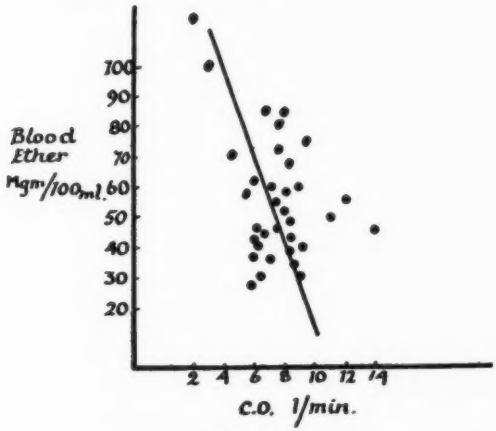


FIG. 9
There is not a close correlation between cardiac output and blood ether concentration in the intact subject.

These results are in sharp contrast with those obtained in the case of the denervated dog heart in which depression of myocardial activity is directly related to strength of dosage with ether.

C. *Thiopentone followed by cyclopropane in oxygen*

Only six cases have been investigated to show the effects of this mixture. All the patients underwent operations of a relatively superficial nature; four were for inguinal hernia, one exploration of right testis and one laparotomy.

The initial values are displayed in table IX. The immediate effect of the anæsthetic mixture is shown in the next table (table X) where it will be seen that an increase in cardiac output and forearm muscle flow occurred, just as in the case of ether. The main difference between these cases and those operated upon under ether lies in the subsequent findings (table XI) which shows that the increases

TABLE IX

*Showing cardiac output, forearm muscle blood-flow, arterial blood-pressure, heart rate and mean right auricular pressure in 6 subjects premedicated with omnopon and scopolamine prior to operation under thiopentone followed by cyclopropane and oxygen.*

| C.O. l/min. | F.B.F. ml/100 ml/min. | B.P. mm. Hg | Heart rate per min. | R.A.P. cm. saline |
|---|---|---|---|---|
| 5.3 | 6.0 | 130/85 | 68 | −3 |
| 4.8 | 3.0 | 110/80 | 64 | −2 |
| 5.5 | 3.5 | 110/85 | 80 | 0 |
| 4.5 | 4.0 | 115/85 | 78 | 0 |
| 4.0 | 5.0 | 110/70 | 75 | −1 |
| 4.7 | 3.5 | 120/80 | 65 | −2 |
| mean 4.8 | 4.2 | | 72 | −1.5 |

TABLE X

*The cardiac output, forearm muscle blood-flow, blood-pressure, heart rate and right auricular pressure in 6 subjects about 10 minutes after induction of anæsthesia with thiopentone followed by cyclopropane in oxygen.*

| C.O. l/min. | F.B.F. ml/100 ml/min. | B.P. mm. Hg | Heart rate per min. | R.A.P. cm. saline |
|---|---|---|---|---|
| 11.0 | 24.0 | 130/75 | 74 | −2 |
| 9.6 | 13.0 | 120/80 | 66 | 0 |
| 8.4 | 17.0 | 115/75 | 84 | 0 |
| 9.5 | 15.0 | 110/70 | 82 | +1 |
| 7.3 | 18.5 | 125/80 | 80 | 0 |
| 7.8 | 16.0 | 120/80 | 75 | 0 |
| mean 8.1 | 17.2 | | 77 | |

are maintained in all except one case. In none of the cases was cyclopropane given in such concentrations as to cause complete respiratory arrest. The results are a little difficult to evaluate because of their small number but they do not conflict with the impressions derived from clinical observation. The increased vascularity of the tissues of subjects anæsthetized with cyclopropane has frequently been commented upon and the general appearance of "pinkness"

TABLE XI

*Showing cardiac output, forearm muscle blood-flow, blood-pressure, heart rate and right auricular pressure during operation under cyclopropane and oxygen anæsthesia. Columns (i), (ii) and (iii) contain values obtained at intervals of about 15 minutes starting half-an-hour after induction of anæsthesia.*

| C.O. 1/min. | | | F.B.F ml/100ml/min. | | | B.P. mm. Hg | | Heart rate per min. | | R.A.P. cm. saline | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (i) | (ii) | (iii) | (i) | (ii) | (iii) | (i) | (iii) | (i) | (iii) | (i) | (iii) |
| 11.0 | 8.6 | 8.0 | 28 | 20 | 16 | 130/75 | 125/70 | 72 | 76 | −2 | −3 |
| 9.6 | 9.8 | 9.0 | 20 | 12 | 18 | 125/80 | 110/80 | 68 | 66 | 0 | −1 |
| 8.4 | 5.2 | 5.1 | 18 | 16 | 12 | 115/75 | 110/70 | 82 | 88 | −1 | −1 |
| 7.8 | 8.0 | 6.0 | 16 | 13 | 10 | 110/70 | 110/70 | 80 | 84 | +1 | 0 |
| 7.6 | 7.5 | 6.0 | 18 | 18 | ? | 120/80 | 120/75 | 84 | 86 | 0 | 0 |
| 8.0 | 7.8 | 7.0 | 16 | 18 | 15 | 120/80 | 120/85 | 76 | 75 | −1 | −3 |

presented by these patients lends good support to these findings. On the other hand, the toxicity of cyclopropane to the dog myocardium and the liability for abnormal heart rhythms to occur make it seem curious that the results in human subjects uniformly indicate a hyperdynamic circulatory state. This and the one case in which cardiac output fell during the second half hour of anæsthesia make it likely that in a larger series more cases with a similar response might be found.

## 3. DISCUSSION

The foregoing experiments clearly show two phenomena which are to be reconciled. First, in the heart lung preparation, these anæsthetic agents lowered cardiac output and higher dosage caused the hearts to fail. Secondly, in the intact human subjects the same agents caused some increase, occasionally considerable, in cardiac output and this in doses of an order which were toxic to the isolated heart of the dog. It will also be seen that one of the most commonly used anæsthetic gases, nitrous oxide, has virtually no effect upon cardiac output when used in the manner described by Gray (1947). (See figure 10.)

Inasmuch as the heart lung preparation is isolated from all its nerve supply save that provided by the junctional tissues, it may safely be concluded that in the dog ether and cyclopropane are myocardial poisons of considerable potency. This conclusion is amply supported by similar results reported by other workers (Cattel, 1923; Moe, Rennick and Freyburger, 1950). The comparatively small amount of ether required to produce this depression is noteworthy; it is in a concentration barely sufficient to produce unconsciousness in the human subject. Concentrations of the order of 100 mg. per 100 ml. of blood which

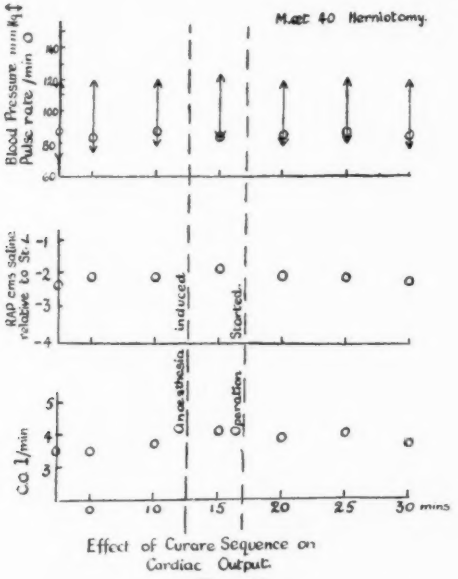


FIG. 10
Typical case showing the relatively small effect of the curare-thiopentone-nitrous oxide sequence on cardiac output, blood-pressure, heart rate and right auricular pressure.

are usual in surgical anæsthesia in humans far exceed the concentrations which were found to be sufficient to produce irreversible damage to the isolated heart of the dog. It must be borne in mind that the canine myocardium may be more sensitive to the toxic effects of these substances than is the human, but it is certainly probable that the effects are qualitatively similar in the two species. These observations apply also to cyclopropane.

The rise in cardiac output which is found in the intact human subject and intact dogs (Blalock, 1927, 1928) on administering either ether or cyclopropane is somewhat

difficult to explain. It is easy enough to see that some rise in output is to be expected when all the measurements are considered together. Briefly, the experiments show that coincident with the administration of an anæsthetic there is a prompt increase in peripheral blood-flow to the limbs together with some acceleration of the heart rate and a slight increase in pulse pressure; the increase in cardiac output fits in with these alterations very well but no clue is afforded as to the mechanism of the changes. On the basis of the animal experiments a fall in output would be anticipated together with a lowering of arterial pressure with or without a fall in peripheral blood-flow. The rise in output which actually occurs, it would seem, must be of nervous reflex origin.

One surprising observation which appears in all the experiments is the absence of any marked rise in central venous pressure. It was unexpected because the clinical appearance of the anæsthetized patient is so often one of marked venous engorgement. The veins on the back of the hand are usually full, and bleeding from veins cut during operation is often brisk. These findings are, of course, consonant with the increased blood-flow through the peripheral tissues, but they also suggest that central venous pressure might be raised. Moreover, in most cases where there is a sustained rise in cardiac output, there is also a raised mean venous pressure, e.g., in chronic anæmia, emphysema, heart disease, thyrotoxicosis and arteriovenous aneurysm. But there is no good reason why this invariably must be so; filling of the right atrium must reach a certain level before measurable rises in atrial pressure need be expected, and it is only when this level has been reached that the thin atrial wall will need to be stretched to accommodate the venous return. It is at this

point that atrial pressure will inevitably rise. In this way, increase of heart rate alone can increase cardiac output without a rise in atrial pressure. Another observation of importance in this connection is that of Cattell (1923) who described the effect of inhalation of ether on the size of the cat's heart. He showed that cardiac dilatation occurred as soon as the anæsthetic was administered and that it continued as the dosage was increased. If this is always true it would seem to be an inescapable conclusion that the normal atrial pressures shown, in the experiments quoted here, are sufficient to stretch the right atrium to an abnormal degree, or in other words that the modulus of elasticity of the heart muscle is lowered by anæsthetics. It is indubitably true that the heart contains more blood just before ventricular systole during anæsthesia than in the normal state, because our results show that stroke output is raised by about 10 per cent. Another important objection to the validity of the atrial pressure measurements must not be overlooked; it is that the saline manometer which was used attached to the end of the cardiac catheter measured, in reality, not filling pressure but the resultant of a number of pressures acting at the tip of the catheter. Important among these are intra-thoracic pressure and any pressures applied to the lungs to maintain respiratory movements. It was assumed that the former remained constant in all those cases where the abdomen was unopened, and the latter was controlled at a measured level as far as was possible. Nonetheless it is felt that too much weight must not be given to the values recorded in the experiments, though *changes* in filling pressure would certainly be recorded.

All the foregoing discussion points to the conclusion that venous pressure is, in all probability, not of great importance in the maintenance of the increased cardiac output.

It remains to consider other possible mechanisms which might play a part. The promptitude of the increase suggested a reflex effect and the parallel increase in peripheral blood-flow might have been the exciting cause. It may be that the chain of events is as follows. As the anæsthetic gains admission to the blood stream a prompt vasodilatation occurs which produces a momentary fall in mean arterial pressure; this fall stimulates the pressoreceptors in the carotid sinus and aortic arch to produce stimulation of the cardiac centre with augmentation of the heart beat. A parallel increase in tone of the splanchnic arterioles decreases blood-flow there, thus preventing too great a capillary bed from being opened up. The net result would be an increase in peripheral blood-flow, and increased cardiac output with but a trifling alteration in blood pressure. It must be admitted that in putting this explanation forward it has been taken for granted that the sinus nerve can affect the cardiac centre, causing it to discharge; this has never been certainly demonstrated. The crucial experiments which would put this beyond doubt have not so far been carried out for technical reasons.

Even if this reflex pathway is operative there still remains to be discussed the increase in peripheral blood-flow which is so constant an occurrence when anæsthetics are administered. That this is due principally to vasodilatation may be inferred from the fact that no rise in blood pressure accompanies it. It may also be inferred from the magnitude of the capillary beds involved that there must be a parallel vasoconstriction in the splanchnic vessels. Experimental evidence for this may be found in the work of Derouaux (1909).

Increased skin temperature and forearm blood-flow are both known to occur during natural sleep; this suggests

that these are connected in some way with diminution of cortical activity mediated perhaps through corticothalamic pathways. Most anæsthetic drugs, ether and cyclopropane among them, also act directly upon the smooth muscle of the arterioles, causing vasodilatation, though rather large concentrations are required for this effect to be apparent; moreover, the rise in blood-flow is so prompt that a nervous mechanism seems to be implicated and in any case it would be rather illogical to suppose that these substances affected one set of arterioles rather than another. In the last stages of anæsthetic poisoning, say with ether, circulatory failure occurs partly through a general dilatation of arterioles in the splanchnic as well as the somatic territories, and this may well be due in part at least to the direct action of the drug. Herrick et al. (1932) have shown that vasomotor tone is abolished in the limbs very early in ether anæsthesia. He considers this to be a local action.

It has been assumed that the first event is the increase in peripheral blood-flow, but it must be noted that there is as yet no evidence whatever that this is really the case and the methods used here are not capable of giving the necessary data to time the increases accurately. Yet the point is an important one, unless the unlikely view be held that the rise in cardiac output and forearm muscle flow are unrelated.

A further point of considerable interest and importance is that cardiac output and forearm blood-flow no less than arterial blood pressures are affected by the duration of anæsthesia. Diagrammatically this is shown in figure 11. This rather constant finding (which was not so noticeable when cyclopropane was used) suggests strongly a toxic action, though this need not be the only factor involved. There is some evidence that oxygen consumption shows a

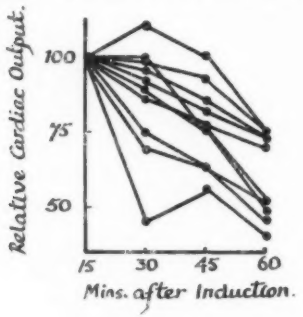


FIG. 11

A correlation is shown between cardiac output under ether anæsthesia at intervals of 15 minutes after induction of ether anæsthesia expressed as percentages of the first value found after induction (Relative Cardiac Output).

somewhat similar, though less consistent, fall as anæsthesia proceeds; this might mean that lowered general metabolism makes a smaller demand for a rapid blood-flow with a consequent fall in cardiac output.

Since writing the above account an important publication by Johnson (1951) has come to hand. In this the author describes experiments in which cardiac output under anæsthesia was determined by the Fick Principle and also by the dye method of Hamilton et al. (1932), which is an independent method. The advantage of the latter is that the volume of circulating blood and that of the blood in the lungs may also be determined. In the main his results support those given here. In addition he concludes that in cases where cardiac output falls a good deal of blood is shunted out of the general circulation into the capillary bed of the lungs. He finds also that myocardial work is often lowered by anæsthetic agents, a finding which fits the evidence given by the animal experiments. It was not considered safe to give figures for cardiac work calculated from the data presented here on account of the errors in both blood-pressure readings and determinations of cardiac output.

## CONCLUSIONS

1. In the dog heart-lung preparations ether, cyclopropane and thiopentone in clinical dosage invariably depress myocardial activity. The relaxant agents, gallamine triethiodide, decamethonium iodide and Win 2747, have no effect.

2. The human subject premedicated with morphia and atropine often showed a slightly raised cardiac output and peripheral blood-flow. This was probably related more to the emotional state of the patient than to the drugs administered.

3. Shortly following the induction of anæsthesia with thiopentone, nitrous oxide and oxygen (50 per cent) and d-tubocurarine chloride there was a considerable increase in forearm blood-flow, without any change in cardiac output. This rise in forearm blood-flow was transient and seemed to be related to injections of thiopentone, but to be independent of gross changes in mean blood pressure.

4. The effect of ether anæsthesia on the intact human subject is initially to produce a very marked increase in forearm blood-flow associated with a variable rise of cardiac output. During the subsequent one hour of anæsthesia the forearm blood-flow falls to levels lower than those found in the pre-anæsthetic period in parallel, with a progressive decline in cardiac output.

5. The effect of cyclopropane on the human subject appeared to follow the same pattern, but the fall in blood-flow and cardiac output over the time observed (75 minutes) was not so great, and in one case was absent.

## SUMMARY

1. The effect was investigated of ether, cyclopropane, thiopentone and certain relaxant agents on the cardiac out-

put as estimated by the Heart-Lung Preparation in dogs.

2. Measurements were made of cardiac output and forearm blood-flow (*a*) in 15 patients anæsthetized with thiopentone, nitrous oxide, oxygen and d-tubocurarine chloride; (*b*) in 10 patients anæsthetized with thiopentone, nitrous oxide, oxygen and ether, and (*c*) in 6 patients anæsthetized with thiopentone and cyclopropane. Cardiac output was estimated by cardiac catheterization, the Fick Principle being employed.

3. In the dog ether, cyclopropane and thiopentone were potent myocardial poisons, but in the intact human subject, in the case of those anæsthetized with ether and cyclopropane, the initial response was a transient increase in cardiac output and forearm blood-flow. This was absent in those cases anæsthetized with thiopentone, nitrous oxide and d-tubocurarine chloride, in whom there was little change.

4. The mechanisms which might underlie these changes are discussed.

5. In the Appendix the accuracy of determinations of cardiac output by the Fick Principle in anæsthetized patients is discussed and accuracy of the methods employed in the present estimations indicated.

We would like to express our grateful thanks to Professor Wells and other members of the staff of the Liverpool Royal Infirmary who have permitted us to carry out this work on their patients, sometimes at considerable inconvenience to themselves.

## APPENDIX

### *The accuracy of determinations of Cardiac Output by the Fick Principle in anæsthetized patients*

The sources of error inherent in the application of the Fick Principle in anæsthetized patients are greater than in the conscious subject (for which see Warren, 1946). This is partly due

to the difficulty of measuring oxygen consumption. In order to assess the accuracy of the spirographic method described in text, paired determinations of oxygen consumption using this method and the Douglas bag technique have been made in which nitrous oxide and cyclopropane were the anæsthetic agents and oxygen the diluent in each case. The following table (A) shows the results. It will be noticed that the agreement is close. The

TABLE A

*Showing replicate determinations of oxygen consumption by the Spirographic and Douglas bag methods in eight different subjects.*

| Spirography ml/min. | | | Douglas bag ml/min. | | |
|---|---|---|---|---|---|
| (a) | (b) | mean | (a) | (b) | mean |
| 241 | 260 | 250 | 250 | 256 | 253 |
| 186 | 185 | 186 | 192 | 202 | 197 |
| 105 | 110 | 108 | 120 | 100 | 110 |
| 290 | 270 | 280 | 300 | 300 | 300 |
| 255 | 265 | 260 | 270 | 265 | 268 |
| 200 | 220 | 210 | 215 | 230 | 223 |
| 186 | 175 | 180 | 180 | 175 | 178 |
| 180 | 185 | 183 | 184 | 164 | 174 |

standard error of the mean of duplicate determinations by the spirographic method is $\pm 10.2$ ml.; the same error by the Douglas bag method is $\pm 8.5$ ml.

The problem of determining the A-V oxygen difference was solved in the case of ether by using Exton's method which has an error of $\pm 0.88$ vols. per cent (S.E. of mean of duplicates). In many cases the actual values agreed more closely than this but this apparent agreement might have arisen by chance and cannot be accepted at its face value. This error is of small consequence when A-V differences are high but when they are less than 20 ml. per litre, as is sometimes the case, an error approaching 10 ml. per litre will introduce an error of about 50 per cent in the final result. For this reason, far reaching conclusions must not be drawn from investigations of this kind, though the results interpreted with proper care may give adequate basis for broad general deductions.

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# THE ROLE OF CHANCE IN THE DEVELOPMENT OF ANÆSTHESIA

By RONALD WOOLMER

CHANCE has always played an important part in scientific progress, and great discoveries have as often resulted from luck as from endeavour. Conversely, many a scientist has been within an ace of making a discovery, but has been led away from it by a trifling circumstance.

In 1846, ether was given to the world as an anæsthetic because a hundred-to-one chance came off. Had not death carried an earlier scientist to an untimely grave, the world might have been given it three hundred years before.

Valerius Cordus was a brilliant and original investigator. He achieved greatness as a chemist, as a botanist, and as a physician. He investigated thousands of botanical species while he was still in his teens, and in his twenties he compiled the first pharmacopœia, which went through thirty-five editions and was translated into eight languages. He was the first to write of sulphuric ether, and his description (Tallmadge, 1925) of its preparation from sulphuric acid and alcohol is a model of clarity, with none of the mysticism and mummery which obscured the writings of his contemporaries. He noted that ether promoted bronchial secretion, but at that time he did not study it further. Paracelsus, his lewd and bombastic contemporary, also wrote of ether, having presumably learnt of it from Valerius Cordus in 1542 when he visited Leipzig, where Cordus was living. Paracelsus wrote of the "sweet sulphur of vitriol" that chickens would eat

it, whereupon they would fall asleep for a moderately long time, and re-awake unharmed (Leake, 1925). It seems as though Paracelsus had discovered its narcotic properties, but his statement that chickens will "eat" a pungent liquid is so odd that it throws doubt upon the whole account. The mind of Paracelsus was so clotted with invisible essences, astral principles, macrocosms and microcosms, sprites and salamanders, that one cannot regard him as a serious investigator. If only Valerius Cordus had applied his clear, incisive brain to the fuller investigation of this ether, he would surely have unlocked its secret. But in 1544 Cordus was in marshy Italy collecting botanical specimens. He was feverish when he reached Rome in September, and he died there a few days later, in his twenty-ninth year.

Three hundred years later, Morton gave the first public demonstration of ether. If we consider the circumstances which attended this demonstration, we cannot fail to be astonished that it was successful. It should have been a more resounding failure than Wells' earlier demonstration of nitrous oxide in the same hospital. Morton claims to have made some experiments—using impure commercial ether—on fish and insects, and on two students (Rice, 1859). In the students, he managed to induce a well-marked excitement stage, but nothing more. This led him to take Jackson's advice and use pure ether, and with this he claims to have experimented on himself. Every anæsthetist who has tried it, however, knows the futility of experiments designed to assess volatile narcotics, in which the assessor is himself the subject; and there seems little doubt that Morton knew virtually nothing of the effects of ether until he first gave it to a patient, for the extraction of one tooth, on 30th September, 1846. This

administration was successful, and Morton was emboldened by this single case to have an account of it sent to the local newspaper. Soon after this first administration—it was certainly within a few days—he went to Warren, senior surgeon to the Massachusetts General Hospital, and persuaded him to let him use general anæsthesia at a surgical operation. This historic administration took place on 16th October, 1846, little more than a fortnight after he had first administered ether to a patient for a half-minute extraction; and there is no evidence that he had used it again successfully in the meantime. Even if he had, it would not have been on more than a few occasions, and then only for short dental extractions.

We know that Morton arrived late at the hospital on the morning of the 16th, because he was waiting for his inhaler to be finished; and he went straight from the instrument maker to the hospital. He therefore had no opportunity to test the apparatus before using it for his demonstration. Let us imagine ourselves in Morton's place. He went, as a man of twenty-seven, not medically qualified, to a famous hospital to demonstrate a new method. His audience, who would have known of Wells' previous failure there, would have been highly critical. The surgeon, Warren, was a man of strong personality. Morton had given ether at most only a few times before, and never with this inhaler. He arrived late to be greeted by Warren with a sarcastic: "Well, sir, your patient is ready." He was expected to induce and maintain anæsthesia with ether on an unpremedicated patient for an operation on the upper part of the neck. No anæsthetist to-day would be such a fool as to put himself in Morton's place.

Now let us consider Warren's (1897) account of the operation.

> "The patient was a young man, about twenty years old, having a tumor on the left side of the neck, lying parallel to and just below the left portion of the lower jaw. This tumor, which had probably existed from birth, seemed to be composed of tortuous, indurated veins extending from the surface quite deeply under the tongue. My plan was to expose these veins by dissection sufficiently to enable me to pass a ligature around them. The patient was arranged for the operation in a sitting posture, and everything made ready. . . . The patient was then made to inhale a fluid from a tube connected with a glass globe. After four or five minutes he appeared to be asleep, and was thought by Dr. Morton to be in a condition for the operation. I made an incision between two and three inches long in the direction of the tumour, and to my great surprise without any starting, crying, or other indications of pain. The fascia was then divided, the patient still appearing wholly insensible. Then followed the insulation of the veins, during which he began to move his limbs, cry out, and utter extraordinary expressions. These phenomena led to a doubt of the success of the application; and in truth I was not satisfied myself, until I had, soon after the operation and on various other occasions, asked the question whether he had suffered pain. To this he always replied in the negative, adding, however, that he knew of the operation, and comparing the stroke of the knife to that of a blunt instrument passed roughly across his neck."

It appears that only four or five minutes were allowed for induction; and it is evident from this and from Warren's account that the patient must have been hovering between the first and second stages of anæsthesia throughout the operation. By rights, it should have been a shambles. His third case actually was. In this, Morton tried for an hour and a half to induce anæsthesia in a patient with a tumour of the breast, and failed completely. If the inhaler had been a little more efficient, so as to bring the patient properly into the second stage, the first case would undoubtedly have been a fiasco, and the introduction of anæsthesia would have been delayed for years. Morton, and the world, were extraordinarily lucky in this first case.

In the development of nitrous oxide there is a parallel and a contrast. Davy ranks with Valerius Cordus as a

scientist and an original investigator. The searchlight of his mind rested briefly on nitrous oxide (Davy, 1800), and passed on, just as had that of Cordus with ether. Allen, who knew of nitrous oxide from Davy, was well aware that it could cause insensibility to pain, and told Astley Cooper so. Paracelsus, who knew of ether from Cordus, was aware of its soporific effect, and told of it in his writings. Yet both agents had long to wait before their properties were used.

The contrast is between the undeserved success of Morton's demonstration of ether and the undeserved failure of Wells' demonstration of nitrous oxide. Wells had given thought and care to the administration of nitrous oxide. He had made opportunities to increase his skill as an administrator before he performed in public; and in his demonstration the operation was the same as in his practice cases. The patient, however, groaned during the extraction (although he later stated that he had felt little pain), and the audience was derisive. Even with modern apparatus, not all dental anæsthetists would be sure of doing better in an isolated case. Fortune was as unkind to Wells as she was kind to Morton; and if care and conscientiousness had had their reward nitrous oxide would have been recognized as an anæsthetic before ether.

Another intellectual giant, Christopher Wren, came very near to the discovery of intravenous anæsthesia. Wren had an insatiable curiosity, and he was a first class experimenter. For his first experiment in intravenous medication in 1656, he used a large dog. He dissected out and ligated a vein, and then made an incision in the vein proximal to the ligature. There was still two hundred years to wait for the development of the syringe, but Wren surmounted this little difficulty by attaching the bladder of an animal

to a goose quill. Quills were of course commonly used in those days as writing implements. A solution containing opium had previously been introduced into the bladder, and it was then a simple matter to inject it into the vein. The account (Oldenburg, 1665) tells us that the dog was soon stupefied, but not killed, and apparently recovered. Having established the technique, Wren continued with his experiments and introduced other drugs, including wine and beer (Sturgis, 1942). But though he sometimes used agents which happened to have narcotic properties, he was not interested in narcosis, and never thought of applying his results to surgery. So another opportunity was lost.

It is often said that advances in science have to wait until the world is ready to receive them: and it might be said that Wren's near approach was therefore of little significance. There were no drugs available in sufficiently pure form to give consistent results—it was not until 1806 that Sertürner succeeded in isolating morphine—and the method of injection would not commend itself to the patient. This argument, however, cannot be extended to the idea of relieving the pain of surgery. Such early attempts as the soporific sponge of Dioscorides indicate that the idea had already taken root, so that Valerius Cordus, had he been spared to continue his work on ether, might well have found fruitful soil.

The scientific development of conduction analgesia, again, had to wait many years for chance to act as a catalyst; and it cannot be argued that the world would not have been ready to receive it earlier. Indeed it is said that the Incas of Peru used cocaine to lessen the pain of trephination (Moodie, 1923). Coca leaves were brought back to Europe about 1850, and Niemann isolated the pure

alkaloid a few years later. During the next twenty-five years its anæsthetic properties were repeatedly demonstrated, but nobody thought of applying them to surgery. Meanwhile, Koller had been looking for a local anæsthetic for his ophthalmic work, but for some reason he had not seen the published reports of the effects of cocaine, even though one of them (von Anrep, 1880) had been published in a widely read periodical in his own language at just about that time. In this report the author actually suggested its use as a local anæsthetic.

Sigmund Freud was investigating the systemic effects of cocaine in psychotic states, and asked Koller to help him (Keys, 1945). As soon as Koller tasted the drug, and felt its numbing effect on his tongue, he realized that this was what he was looking for. At the Heidelberg Ophthalmological Congress in 1884 it was shown in public, and within a year it was being used all over the world for many types of conduction analgesia. Indeed, its introduction caused almost as great a sensation as had that of ether forty years before.

Once again, one is impressed by the slowness of the development of anæsthesia, and by its dependence on chance. A study of this development engenders no feeling of an increasing pressure from many quarters inexorably squeezing out the secrets of nature, as does a study of the development of the physical sciences. Rather, it gives the impression of a number of secrets buried near the surface, with several clues pointing towards each spot, being accidentally stumbled on by a heavy-footed searcher looking for something quite different. Who knows what glittering secrets may lie buried just beneath the ground for us to stumble on?

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## SOCIETY OF ANÆSTHETISTS OF SOUTH WALES

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*Friday, 4th April*, 7.30 *p.m.*

Anæsthetic films will be shown at Cardiff Royal Infirmary. Coffee and light refreshments will be served.

*Saturday, 14th June.*

Clinical Meeting at Sully Hospital. All day meeting.

*Friday, 28th November* (*Probable date*).

Dinner Meeting with Guest Speaker.

Dinner Meetings, i.e. the last mentioned meeting and the Annual General Meeting, are free to full members. A charge, usually 7*s.* 6*d.*, is made for dinner to Registrars.

## *NOTES AND COMMENTS*

### A SLOTTED BRONCHOSCOPE FOR THE INTRODUCTION OF BRONCHIAL BLOCKERS

As the illustration (figure 1) shows, this bronchoscope has a segment of its lumen removed along its whole length. This does not interfere with its use in any way. When the blocker has been inserted, the slot enables the bronchoscope to be removed without disturbing the blocker. It is unnecessary for the whole of the blocker to be threaded through the bronchoscope when the latter is being removed, as is the case with the usual bronchoscopes; the blocker is, so to speak, "peeled off" the bronchoscope through the slot. A battery in the handle and the usual bulb at the tip of the instrument provide adequate illumination.

SOLOMON N. ALBERT
*Beirut, Lebanon*
*(Now at George Washington University Hospital, Washington, D.C.)*

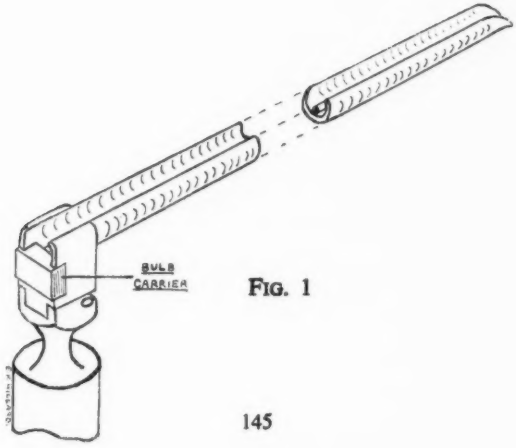


FIG. 1



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ENDOTRACHEAL CONNECTIONS

The Endotracheal Connections illustrated (figure 2) have been elaborated over a period of years at the Glasgow Royal Infirmary, and have proved satisfactory.

The main features are the exceptionally wide bore, plus the fact that direct contact can be made with the anæsthetic apparatus. Although the connections will fit directly to the standard angle-piece or Y piece on the Coxeter-Mushin apparatus, a special angle-piece is recommended. It is stoutly built, keeping its shape better, and has an expiratory valve or alternately a cap fitted in line with the serrated end of the connection, so that either can be removed for suction purposes. The angle-piece is also made with slight modifications to fit the Waters' absorber, or any type of apparatus in common use.

When the connections are used with the Waters' absorber, it is desirable in certain cases to insert a short extension piece between the angle-piece and the soda lime crystals. This has been made of rubber with metal tapered fittings, and is of sufficiently wide bore not to increase the resistance to respiration. Detachable rings with eyeholes,

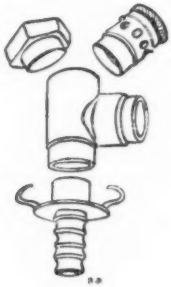

FIG. 2

placed at each end of the cannister, ensures the latter being easily secured to a pillow by means of towel clips.

Curved connections for nasal or oral use are included in the set. They are used in conjunction with the extension piece and have been found useful in operations on the face and E.N.T. surgery.

A four-tailed rubber harness holds the endotracheal connections and the corrugated tubing of the anæsthetic apparatus or the extension piece securely in position by means of suitably placed hooks.

All the separate components, i.e. the connections, the angle-piece, expiratory valve, cap, and extension piece, have tapered fittings to facilitate speedy assembly.

The connections are primarily intended for adults, and although originally four sizes were envisaged, it has been found that the two larger sizes, i.e. sizes 3 and 4, have proved adequate.

The various parts described were made for me by A. Charles King, Ltd., London, and I wish to thank especially Mr. C. G. Dowse of that firm for the valuable assistance given.

ALEX C. FORRESTER
*Glasgow Royal Infirmary*

## FROM THE MORBIDITY CONFERENCE

### *Intubation Hazards*

A 65-year-old female patient was for nephrectomy. Oral intubation was attempted following gallamine triethiodide 60 mg. and thiopentone 0.4 g. In spite of good relaxation it was difficult to visualize the cords with a Macintosh laryngoscope. To complicate matters the light went out on several occasions at the critical moment. However,

after much manipulation the tube was passed and the anæsthetic continued satisfactorily.

The pharyngeal reflex was active at the end of the operation, the cuff of the tube was deflated and it was found impossible to withdraw the tube by gentle traction. After several attempts direct laryngoscopy was performed. A strip of mucosa from the posterior surface of the epiglottis was found to be detached at its proximal end, bent over backwards and wedged between the anterior side of the tube and the cords, thus anchoring the tube firmly in position. By applying suction to this piece of mucosa it was possible to remove it intact and the tube slipped out easily. The strip of mucosa, which still remained attached to the epiglottis at its distal end, was gently reapplied in its original position. In spite of close questioning the patient never made any complaint of a sore throat during her stay in hospital and her convalescence was uneventful.

Failure of the light of the laryngoscope undoubtedly caused this accident. It is impossible to say whether the mucosa was removed by the blade of the laryngoscope or by the tip of the endotracheal tube, which was rather stiff.

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A young adult male was brought to the theatre with a bleeding tonsillar bed—his tonsils having been removed by dissection earlier in the day. The oro-pharynx was sucked out and 0.4 g. thiopentone and 80 mg. gallamine triethiodide were administered intravenously. A lubricated No. 7 Magill tube was passed through the right nostril and a Macintosh laryngoscope was inserted into the mouth. The tip of the tube was not visible and did not appear in spite of its being pushed about one inch farther in. It was then noticed that the mucosa of the right pharyngeal wall below

the tonsil bed was undulating in a most alarming manner, and it was realized that the tip of the tube had entered the tonsillar bed and was stripping up the mucosa. The tube was withdrawn and re-inserted without further trouble. No post-operative complications were observed.

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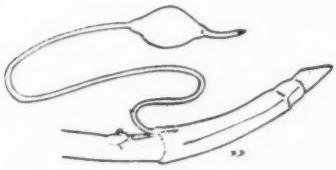

FIG. 3

Figure 3 shows another cause of difficulty in intubation. The tube from the pilot balloon had become detached from the main tracheal tube and the small piece of rubber left at the sealing protruded behind the cords and impeded the clear withdrawal of the endotracheal tube.

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*Intra-arterial Injection*

The danger of injection of thiopentone into an artery in the ante-cubital fossa is well recognized, but in this case an intra-arterial injection of saline was given inadvertently into the radial artery. A patient needing a saline transfusion after an operation was found to have collapsed veins. A tourniquet was applied lightly in the forearm and he was asked to open and close his hand to improve the local circulation. A little while later there appeared a prominent vessel about two inches above the wrist on the radial side of the front of the forearm. After testing for pulsation a needle was introduced and the saline tube connected on

to it. As soon as the tourniquet was released the level of saline in the safety drip began to rise and air bubbles were seen to enter the saline bottle from the tube. It was realized at once that the needle was in the radial artery. The needle was removed and a pressure bandage applied with dressing.

This case shows that under these conditions (tourniquet) the radial artery could be mistaken for a vein.

## *CORRESPONDENCE*

### ACTION OF THE INTERCOSTAL MUSCLES

Sir,

Dr. Primrose (*Brit. J. Anæsth.* (1952), **24**, 3) is to be complimented on his investigation of some of the statements that have been made in the past concerning the action of the intercostal muscles, particularly as he approaches the subject not only from the experimental but also from the comparative angle.

Some of his conclusions differ little from the statements found in current anatomical textbooks. Thus Gray's *Anatomy* (1949) states that the intercostal muscles prevent the intercostal spaces being drawn in or bulged out during respiration and that both groups act as elevators of the ribs. Buchanan's *Manual of Anatomy* (1946) contains a similar description. There seems to be fairly general agreement that one of their main actions is to resist the pushing out or pulling in of the spaces by changes of intra-thoracic pressure. The main issue arising from Dr. Primrose's paper is the role of the intercostals in moving the ribs, whether they successively separate and approximate the ribs, or, as most modern textbooks suggest, are both involved in the elevation of the ribs, particularly in quiet respiration. As this is a question of considerable importance the evidence must be examined critically and, with this in view, I should like to make some comments.

Concerning the evidence that the intercostal muscles cannot be seen to contract when exposed in mastectomy, I doubt whether it would be possible to see contractions in such short muscles. It is even less likely that the contractions of the fibres of the cut intercostal muscle, which have

already become much retracted under their own elasticity, can be perceived. Contractions in the longer neck muscles, exposed in cerebellar operations, may well be evident. Dr. Primrose describes the latter as " strange associates in the respiratory act ". None of these muscles gain direct attachment to that part of the thoracic cage which moves in respiration. I fail to see why these should be associates in the act.

Dr. Primrose does not think that Gessel's view that there are " marked individual differences in the breathing pattern " is tenable. A similar view is expressed in Gray's *Anatomy* which states, " The range and character of the movements of the thoracic parietes exhibit a very striking individual variation ", and " Variations which may be dependent on the conformation of the thoracic skeleton, on habit and occasionally on other factors ". Are there no such variations and are there no sex differences in the pattern of respiration? May not the mechanism vary with posture, and may not the mechanism in, say, a dog lying on its side differ from that seen when it is standing?

Findings in quadrupedal mammals are not of necessity applicable to bipedal man, nor are observations on the anæsthetized necessarily applicable to the unanæsthetized. The external muscles of respiration, to use Bell's term, are in all probability vastly different in the quadruped and biped. Muscles attached to both thorax and upper limb in a quadruped are more or less ideally placed to act on the thoracic cage; in man on the other hand with his free upper limb the same muscles may act from the relatively fixed chest.

The experiments in which three ribs and the intervening intercostal muscles are isolated from the first and more posterior ribs must not be allowed to pass without com-

ment. In quiet respiration the first rib is generally thought to be relatively immobile and to serve as a fixed point from which the succeeding intercostal muscles act. Is this conception correct? The first rib is provided with a well developed levator costæ muscle. This criticism would lose its force if the attachments to the first rib were not interfered with. Again the experiment surely tends to interfere with the normal tonus of the intercostal muscles. There is no longer any pull against these muscles and the stretch reflex is abolished.

As regards the immobility of the chest in the aged rabbit, is this true also of old men? When the chest becomes immobile, what becomes of the levatores costarum? Do they atrophy or degenerate?

Finally the findings of Bronk and Ferguson remain unexplained. "The rhythmic groups of impulses in the fibres to the external intercostal muscles are generally associated with inspiration; in the fibres to the internal intercostal muscles with expiration." How may this be explained?

Dr. Primrose's paper will arouse much interest and we must be indebted to him for again pointing out that not only are the central controls of respiration complex and ill understood, but so also are the peripheral mechanisms. Further electromyographic studies should prove of great value in this field and it ought to be possible, even in man, to record changes simultaneously in the internal and external intercostal muscles. Another possible approach would be more observations on the effects of curare which is said to paralyse progressively groups of muscles.

D. V. DAVIES
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*St. Thomas's Hospital Medical School)*

Sir,

In reply to the comment of Prof. Davies upon the difficulty of observing visible contraction of the intercostal muscles when damaged during mastectomy, the findings of Bronk and Ferguson tend to show that the tonicity of these muscles is rhythmical and not fixed, so that active movement, if present, should be visible. This does not occur.

The association of the epimeric muscles with breathing in the cerebellar cases mentioned is not anatomical but is a cybernetic one and illustrates the faculty of the central nervous system for switching motor impulses into unusual channels to achieve a definite purpose.

The question of individual variations in the character or pattern of breathing are again fundamentally nervous in response to the many influences that may modify it. The sex differences are quite recognizable, but tend to be less marked in quiet breathing in the female than used to be the case when dress was more restrictive. Gestation becomes the natural restriction which emphasizes the female type of breathing.

Posture in the case of the dog must influence the breathing. Lying anæsthetized on its side or back it will require very much less respiratory exchange than if able to stand. It is probably on this account that intercostal action according to Gessel appears so desultory.

It is quite true that findings in the quadruped may not be strictly applicable to the orthograde man, but the intercostals are such a fundamental and primitive group of muscles that any error of interpretation of their action might be very small.

The movement of the first rib in quiet respiration can be little different to that of the succeeding ribs which are also

fixed to the sternum. The movement of the manubrium sterni determines the angular excursion of the first rib and, according to Keith, this is its only movement. It is, therefore, no more a fixed point for intercostal action than are the succeeding ribs which move along with it. Fixity for such action can only be found in the neck above or in the abdominal resistance below. Relative fixation of the first rib would lead to a great strain on the lower ribs in a grouped action such as we have seen in the rabbit, and of this there is no evidence.

Concerning the immobility of the chest in the elderly, dissecting room evidence would tend to show that the levatores muscles sink into the same condition as is presented by the intercostals at any time, and they appear to be largely neglected by the central nervous system as effective muscles. They do not degenerate beyond this point.

The Bronk and Ferguson experiments which are so much more limited than those of Gessel, who has investigated the entire range of intercostal muscles, would serve to show that tonicity is maintained in both phases of breathing by the two muscles alternately. This again may be a purely nervous manifestation related to the quiet breathing of anæsthesia, to be altered and overstepped at once if respiratory needs call for increased effort. This is, however, merely " explanation ".

In conclusion, it should be stated that the scope of this investigation was intended to be very narrow, but discussion has broadened the matter out into regions in which the crude methods adopted to show the visible activity of muscle in a gross movement can have no place in a purely natural system of movement. Living things seem to be too susceptible to the effects of artificial interference to give uniform and reliable results when examined. The prospects

offered by neuro-physiology would appear to be more favourable in the more complete understanding of this and similar problems.

Dr. Mushin, if I remember correctly, at the meeting of the Anæsthetic Section of the Royal Society of Medicine, at which this matter was considered, commented upon the fallacy of intercostal paralysis as a sign of deepening anæsthesia and mentioned that the idea was also held by Snow and Clover in the past, and thought that the sign could not be so easily dismissed on the grounds presented.

It might be stated in reply that such celebrities would have been quick to admit that the basis of their observation, founded as it was upon the anatomical convention of intercostal action, was not supported by surgical demonstration, had this been available to them.

W. B. PRIMROSE
(*Glasgow Royal Infirmary*)

## INTRAVENOUS PETHIDINE IN ANAESTHESIA

Sir,

Dr. Pearce's interesting paper "Intravenous Pethidine in Anæsthesia", appearing in your issue for last October, refers to a practice which is followed by many anæsthetists, but which—I submit—is wrong.

Dr. Pearce states: "In the earlier part of this series relaxants were used only when specifically indicated, but more recently they have been employed to lessen the likelihood of reflex movements occurring, as may sometimes happen in such light anæsthesia." In departing from the rigid principle of using relaxants only when specifically indicated, he is setting his foot on the downward path made slippery by the previous descent of too many anæsthetists.

Relaxants are now given, it appears, to stop reflex movements. There are two ways in which they can do this. They can depress ganglionic activity in the reflex arc, or they can paralyse the striped muscle effectors. It has been shown that d-tubocurarine, in the doses normally used, has little effect on ganglionic activity, and gallamine and decamethonium have still less, so that it is evidently only by paralysing the effectors that these reflex movements are suppressed.

But it is precisely by these reflex movements that the anæsthetist should be warned that *anæsthesia* is inadequate and must be deepened with a centrally acting drug. Indeed, Dr. Pearce seems to recognize this in an earlier section, when he says: "In a few cases reflex movements of the fingers occurred when the towel clips were applied, but a pause of a further minute or two, with, in a few cases, a small supplementary dose of pethidine always produced a stable anæsthetic level."

It seems to be not generally realized by the teachers of anæsthesia—or at least not generally taught—that there are three stages of curarization, though admittedly the boundary between them is not clear cut. First, there is the atony of Bremer, in which the muscle has lost its postural tone and is therefore relaxed, but in which it can contract as a result of voluntary or reflex nervous activity. Next, there is the paralysis of Vulpian, in which the muscle is toneless and will not respond to voluntary or reflex nervous activity, but will respond to electrical stimulation of the motor nerve. Lastly, there is the paralysis of Claude Bernard, in which the muscle will respond to nothing but direct stimulation of its fibres.

The first stage, the atony of Bremer, is all that the

anæsthetist needs to produce. If the patient's sensory apparatus is properly anæsthetized by centrally acting drugs, there will be no voluntary or reflex nervous activity (which would result in the release of more acetylcholine), and muscular relaxation will be complete. If the patient is not adequately anæsthetized he will be able to signal the fact to the watchful anæsthetist by "reflex movements of the fingers when the towel clips are applied", or by small movements of the mouth or eyebrows. The appropriate remedy will then be more anæsthetic (the term is intended to include pethidine), *not* more relaxant: though more relaxant would certainly stop the movement by producing the paralysis of Vulpian or of Claude Bernard. The amount of anæsthetic added should be no more than enough to make the sensorium insensitive to the stimulus being applied. This will not be sufficient to contribute significantly of itself to muscular relaxation.

In this way the principles of never using more of *any* drug than is needed to produce the required therapeutic effect, and of never using any drug without a clear and definite indication, would be honoured in the observance. It is to be feared that many anæsthetists today honour them only in the breach.

It is true that the method I advocate calls for great vigilance from the anæsthetist. That is one of its advantages. Another advantage is that it steers a course well away from the horror of the curarized but unanæsthetized patient, feeling pain but unable to protest, to which the attention of anæsthetists has already been drawn.

The argument that no demonstrable harm appears to result from the much larger doses of relaxants which are commonly given is irrelevant. The conscientious anæs-

thetist should impose on himself the exacting duty of using these drugs in the smallest effective dosage.

RONALD WOOLMER
(*Department of Anæsthetics, Bristol*)

Sir,

I am surprised that my paper dealing as it did with the use of pethidine in nitrous oxide anæsthesia, should have prompted Dr Woolmer to raise the issue of the use of excessive amounts of relaxant drugs in combination with inadequate anæsthesia.

In actual fact no mention was made in my article of the quantities used of the various relaxant drugs, but, in those cases in which they were used to limit involuntary muscle activity rather than for any specific exigency of the operation, almost without exception operations for hernia, the mean amount of gallamine used was 81 mg., and the mean duration of anæsthesia 44 minutes.

In conclusion I would refer Dr. Woolmer to the closing paragraph of that section of my paper entitled "Technique-using Muscle Relaxants". This reads "Gallamine has one minor disadvantage in that it produces a tachycardia in a high proportion of cases, thus rendering the decision as to when more pethidine will be required somewhat difficult. If, however, a hand is kept under observation, slight movement of the fingers will usually indicate the necessity".

This observation could hardly have been made on patients receiving excessive amounts of relaxant drug.

CECIL PEARCE
(*Sheffield Royal Infirmary*)

## REVIEWS

*Observations on the General Effects of Injury in Man with special reference to wound shock.* By R. T. GRANT and E. B. REEVE. Medical Research Council Special Report Series No. 277. Published by: Her Majesty's Stationery Office. 313 pages, 51 tables, 19 figures. Price 8*s*. 6*d*.

The authors begin and end their work by deploring the use of the unqualified term "shock", which they find themselves unable to define. Your reviewer has, for 10 or 12 years, so far discouraged its use that he has asked that it should always be written, not only in inverted commas but also upside down, thus, "ʞɔoɥs", to emphasize its lack of precise meaning.

The work, which occupies 300 pages of close print, is in four sections devoted respectively to limb injuries, abdominal injuries, discussion, and clinical pathology. The reader who is not himself a researcher in this field is well advised to read the third section, the discussion, first. The other sections are too particular for easy reading and the conclusions to be drawn are so broad that the general reader may safely skip much of the detail. On the contrary, other research workers will appreciate the meticulous case records. Further contributors can judge for themselves the value of the evidence on which the authors' conclusions are based and, if they wish, put their own interpretations on the same facts.

The section on limb injuries comes quickly to the forthright statement that loss of blood is the cause of the wounded man's state of illness. The clinical methods of

assessment of the amount of blood lost are clearly described and the corresponding amounts of transfusion are indicated. The importance of early, quick and adequate transfusion is constantly emphasized. Other factors such as the psychogenic element and the effects of surgery are kept in fair perspective. The anæsthetist's contribution to the amelioration or aggravation of the conditions found is, perhaps, somewhat cursorily dismissed. Attention is drawn to the danger of vomiting in unprepared patients and to the artificial raising of blood pressure by respiratory obstruction. The question of the choice of anæsthetic agents is not fairly faced. These apparent shortcomings are no doubt due to the lapse of 7 years between the completion of the work and the publication of this report. Anæsthetic technique has undergone a revolution in that time and if more had been written it would, to-day, have read like history.

It is interesting to see how much more difficult the authors find it to dispose of the problems of illness arising from abdominal injury. The picture is at once complicated by fresh variable factors. But they stick to their guns and conclude that haemorrhage and its control are of prime importance. Seven years ago infection and peritonitis were uncontrolled by the antibiotics which to-day we take for granted and the time is thus already ripe for an extension of the work covered by this section.

Burns, the crush syndrome, and other causes of conditions resembling wound shock are matters with which the authors have not been concerned.

To summarize briefly, for the researcher this publication is a valuable work of reference; for the student it is an encouragement in that it roundly dismisses much that failed to make sense; for the clinician it embodies a simple

theory which will, it is to be hoped, be abstracted into a shortened form for easier assimilation; for the carping critic it is a cause for regret that it did not appear a number of years ago.

*The Health Services. Some of their Practical Problems.* With an introduction by Henry Lesser, C.B.E. Published for the Institute of Public Administration by George Allen & Unwin Ltd., London. Pp. 136. 10*s.* 6*d.*

An important conference arranged by the Institute of Public Administration was held a year ago in London. At this conference various general aspects of the National Health Service were discussed by experts in their respective fields. This book consists of most of the papers read at this conference, revised in the light of discussion there, or of subsequent developments. The papers, it is true, are mainly of administrative interest, but if the anæsthetist is to understand his own position in the general scheme he must be interested in this aspect too. Two chapters that can be recommended to him are those on "Functions of a Regional Hospital Board" and "Problems of Hospital Administration". Though nowhere mentioned specifically, the anæsthetist will easily identify himself under the general heading of consultants and will find that much that was obscure becomes clear.

Most anæsthetists could glance through this book with profit. Its particular appeal will be to those who come into much contact with the administrative side of the National Health Service.

*The English Pioneers of Anæsthesia (Beddoes: Davy: Hickman)* by F. F. CARTWRIGHT. Published by John Wright & Sons Ltd. Pp. 338, 20 plates. Price 21*s.*

This book deals with events in England at the end of the 18th and beginning of the 19th centuries which played an important part in the subsequent discovery of anæsthesia in America. It shows how near and yet how far English workers were from making this vital discovery. It is an excellent bibliography of the three pioneers Beddoes, Davy, and Hickman, and does not confine itself simply to their connection with anæsthesia. Some of the sidelights on the life of Sir Humphry Davy are particularly interesting. The story is made complete by the concluding essay, which deals with the work of Coulton, Wells, and Morton, and logically traces the link between Coulton's demonstrations in Hartford and Thomas Beddoes' Pneumatic Institution in Bristol.

Quotations are, of necessity, numerous, and these make very interesting reading. This book is obviously the result of many years' study and research into the lives of pioneers who receive only very brief mention in the standard history books of anæsthesia. It will prove of benefit not only to anæsthetists but also to those interested in the early history of the physiology of respiration.

*Anæsthetics and Anæsthesia for Nurses.* By W. J. FINNIE, M.B., Ch.B., B.Sc., D.A. Published by *Nursing Mirror.* Pp. 110, 36 illustrations. Price 7*s.* 6*d.*

This volume is based upon a series of articles first published in *Nursing Mirror,* and is a preliminary step in the provision of a reference book in anæsthetic matters for nurses and indeed for theatre orderlies. The material is well arranged and information of value and interest to the

nurse is concisely and clearly expressed, particularly in Sections 5 and 6. Diagrams throughout, if on occasion a little crude, are most helpful and explanatory, but photographs of apparatus and equipment are too crowded to show detail. It is to be regretted that the author ignores completely the post-operative duties connected with the nursing of the unconscious patient. To many the most important part played by the nurse only begins when the recovering patient is handed over to her by the anæsthetist. Perhaps the author will extend his useful contribution in a later edition to include the post-operative period and at the same time correct the rather inaccurate accounts of the actions of curare and neostigmine. Such criticisms apart, this book is a valuable addition to the Nurses' Library and goes a long way towards meeting the increasing knowledge of anæsthetic detail which is expected from the modern nurse.